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Ambient Water Quality Criteria: Lead

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LEAD

Ambient Water Quality Criteria

Criteria and Standards Division
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CRITERION DOCUMENT

LEAD

CRITERIA

Aquatic Life

For lead, the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.51 \ln(\text{hardness}) - 3.37)}$" as a 24-hour average (see the figure "24-hour average lead concentration vs. hardness") and the concentration should not exceed "$e^{(1.51 \ln(\text{hardness}) -1.39)}$" (see the figure "maximum lead concentration vs. hardness") at any time.

For saltwater aquatic life, no criterion for lead can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the protection of human health from the toxic properties of lead ingested through water, the water criterion is 50 µg/l.

BIBLIOGRAPHIC INFORMATION

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Criteria and Standards Div.

Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for lead. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regu, ...

KEYWORDS: *Water quality, *Toxicology, *Lead(Metal), *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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Introduction

Lead is a soft gray, acid-soluble metal. It is used in electroplating, metallurgy, and the manufacture of construction materials, radiation protective devices, plastics and electronics equipment. The solubility of lead compounds in water depends heavily on pH and ranges from about 10,000,000 µg/l of lead at pH 5.5 to 1 µg/l at pH 9.0 (Durum, 1973). Inorganic lead compounds are most stable in the plus two valence state, while organolead compounds are more stable in the plus four state (Standen, 1967). Lead concentrations in seawater have been reported at 0.03 µg/l (Tatsumoto and Patterson, 1963) and in fresh waters from 2 to 140 µg/l, with a mean of 23 µg/l (Kopp and Kroner, 1967).

Lead reaches the aquatic environment through precipitation, fallout of lead dust, leaching from soil, street runoff, and both industrial and municipal wastewater discharges (U.S. EPA, 1976). It can be removed from the water column by adsorption to solids or chemical precipitation or coprecipitation.

In the aquatic environment, lead has been reported to be acutely toxic to invertebrates at concentrations as low as 450 µg/l (Biesinger and Christensen, 1972) and chronically toxic at less than 100 µg/l (Biesinger and Christensen, 1972). The comparable figures for vertebrates are 900 µg/l for acute toxicity (Brown, 1968) and 7.6 µg/l for chronic toxicity (Davies, et al. 1976). Toxicity is also affected by water hardness (Tarzwell and Henderson, 1960; Pickering and Henderson, 1966). Hard water is protective of organisms exposed to lead.

Bacterial action has been shown capable of converting inorganic lead to organic forms (Wong, et al. 1975; Silverberg, et al. 1976). Algae reportedly can concentrate lead in their tissues to levels as much as 31,000 times ambient water concentrations (Trollope and Evans, 1976). Since lead is an element, it will not be destroyed and may be expected to persist indefinitely in the environment in some form.

Lead has been shown to be teratogenic in animals (McLain and Becker, 1975). Lead exposure has been reported to decrease reproductive ability in men (Lancranjan, et al. 1975) and women (Lane, 1949). It has also been shown to cause disturbances of blood chemistry (Roels, et al. 1978), neurological disorders (Perlstein and Attala, 1966; Byers and Lord, 1943), kidney damage (Clarkson and Kench, 1956) and adverse cardiovascular effects (Dingwall - Fordyce and Lane, 1963).

REFERENCES

Biesinger, K.E., and G.M. Christensen. 1972. Effect of various metals on survival, growth, reproduction, and metabolism of Daphnia magna. Jour. Fish. Res. Board Can. 29: 1691.

Brown, V.M. 1968. Calculation of the acute toxicity of mixtures of poisons to rainbow trout. Water Res. 2: 723.

Byers, R.K. and E.E. Lord. 1943. Late effects of lead poisoning on metal development. Am. Jour. Child. 66: 471.

Clarkson, T.W., and J.E. Kench. 1956. Urinary excretion of amino acids by men absorbing heavy metals. Biochem. Jour. 62: 361.

Davies, P.H., et al. 1976. Acute and chronic toxicity of lead to rainbow trout, Salmo gairdneri, in hard and soft water. Water Res. 10: 199.

Dingwall-Fordyce, J., and R.E. Lane. 1963. A follow-up study of lead workers. Br. Jour. Ind. Mech. 30: 313.

Kopp, J.F., and R.C. Kroner. 1976. Trace metals in waters of the United States. Fed. Water Pollut. Control Admin. U.S. Dep. Inter., Cincinnati, Ohio.

Lancranjan, I. et al. 1975. Reproductive ability of workmen occupationally exposed to lead. Arch. Environ. Health 30: 396.

Lane, R.E. 1949. The care of the lead worker. Br. Jour. Ind. Med. 6: 1243.

McLain, R.M., and B.A. Baker. 1975. Teratogenicity, fetal toxicity and placental transfer of lead nitrate in rats. Toxicol. Appl. Pharmacol. 31: 72.

Perlstein, M.A., and R. Atlala. 1966. Neurologic sequelae of plumbism in children. Clin. Pediat. 6: 266.

Pickering, Q.H., and C. Henderson. 1966. The acute toxicity of some heavy metals to different species of freshwater fishes. Air Water Pollut. Int. Jour. 10: 453.

Roels, H.A., et al. 1978. Lead and cadmium absorption among children near a noferrous metal plant. A follow-up study of a test case. Environ. Res. 15: 290.

Standen, A., ed. 1967. Kirk-Othmer encyclopedia of chemical technology. Interscience Publishers, New York.

Tarzwell, C.M., and C. Henderson. 1960. Toxicity of less common metals to fishes. Ind. Wastes. 5: 12.

Tatsumoto, M., and C.C. Patterson. 1963. The concentration of common lead in seawater. Page 74 in Earth science and meteorites. North Holland Publishing Co. Amsterdam.

Trollope, D.R., and B. Evans. 1976. Concentration of copper, iron, lead, nickel, and zinc in freshwater algae blooms. Environ. Pollut. 11: 109.

U.S. EPA. 1976. Quality criteria for water. Off. Water Plan. Stand. U.S. Environ. Prot. Agency, Washington, D.C.

Wong, P.T.S., et al. 1975. Methylation of lead in the environment. Nature 253: 263.

AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The toxic effects of lead have been extensively tested on a wide variety of freshwater organisms. Representative test animals used to determine these effects included fish from six different families (Salmonidae, Cyprinidae, Catostomidas, Ictaluridae, Poeciliidae and Centrarchidae); invertebrate species were represented by rotifers, annelids, snails, cladocerans, copepods, isopods, mayflies, stoneflies and caddisflies; and plants from the algal, desmid and diatom groups. Consequently, the available data base is quite large and clearly demonstrates the relative sensitivity of freshwater organisms to lead.

Acute Toxicity

As shown in Table 1, 15 LC50 values were available for eight species of fish. All acute tests except one were conducted for 96 hours, so only one test involving the red shiner needed adjustment for test duration. Of the 15 acute exposures only three were reported to be flow-through experiments and of these three only two (Davies, et al. 1976 and Holcombe, et al. 1976) reported measured values of total lead; therefore, most of the LC50 values in Table 1 were adjusted for static exposures and unmeasured test concentrations.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The first three soft water fathead minnow acute tests were conducted with lead chloride, and unadjusted LC50 values ranged from 2,400 to 7,330 µg/l (Table 1). The close agreement between these tests demonstrates that lead LC50 values for fish can be reproduced with reasonable accuracy. The fourth soft water fathead minnow test (Table 1) was conducted with lead acetate and the calculated LC50 value agreed closely with the lead chloride exposures. These results demonstrate that these different lead salts have similar LC50 values. All other tests with fish were conducted with either lead chloride or lead nitrate.

Acute tests have been conducted with lead in both hard and soft water with rainbow trout, fathead minnows and bluegills (Davies, et al. 1976 and Pickering and Henderson, 1966). Results from these tests showed that the adjusted LC50 values for lead were greatly different in hard and soft water and varied by a factor of 237 times for rainbow trout, 65 times for fathead minnows and 19 times for bluegills (Table 1). Another example of hardness related lead toxicity to fish was reported by Tarzwell and Henderson (1960). These authors conducted 96-hour exposures of fathead minnows to lead in hard (400 mg/l) and soft (20 mg/l) water. Results from the soft water test are shown in Table 1. The hard water exposure was not included because an LC50 value was not obtained within 96-hours; however, this test did show that the hard water LC50 value was greater than 75,000 µg/l which meant that the difference between hard and soft water exposures varied by a factor greater than 31 times. Hale (1977) conducted an acute exposure of rainbow trout to lead and obtained an adjusted LC50 value of 6,160 µg/l. This value is almost 6 times greater than the LC50 value obtained for rainbow trout in soft water by Davies, et al. (1976). Hale (1977) did not report water hardness; however, alkalinity and pH were reported to be 105 mg/l and 7.3, respectively, which suggests that this water was probably harder than the test water used by Davies, et al. Acute values obtained by Wallen, et al. (1957) for the red shiner and mosquitofish were also quite high; however, the authors did not report hardness and both tests were conducted in turbid water containing suspended clay particles at approximately 300,000 µg/l.

Following the Guidelines, an exponential equation describing the relationship of toxicity to hardness for each species was fit by least squares regression of the natural logarithms of the toxicity values and hardness. For lead, sufficient acute toxicity data and hardness ranges were available for rainbow trout, fathead minnows, and bluegills to fit regression equations. The slopes of these equations ranged from 1.01 for bluegills to 2.16 for rainbow trout, with a geometric mean of 1.51.

As a measure of relative species sensitivity to lead, logarithmic intercepts were calculated for each species by fitting the mean slope (1.51) through the geometric mean toxicity value and hardness for each species. These intercepts varied from 2.60 for brook trout to 5.23 for goldfish, with a mean intercept of 3.86 for all six fish species. This variation in logarithmic intercepts indicates a range of species sensitivity to lead of only 14-fold when adjusted for hardness effects. The adjusted mean intercept (2.50) is slightly lower than that for the two salmonid species tested. Thus the Final Fish Acute Value is given by: $e^{(1.51 \ln(\text{hardness}) + 2.50)}$.

The acute toxicity data for invertebrate species (Table 2) contains 10 values for 9 species. Only one test was conducted for 96 hours; however, the standard test for cladoceran and copepods is 48 hours so these exposures needed no adjustment for test duration. None of the acute tests shown were flow-through exposures and only one (Brown, 1976) involved measured concentrations of total lead.

Whitley (1968) reported 24-hour LC50 values of 49,000 and 27,500 µg/l for sludge worms obtained from tests conducted at pH levels of 6.5 and 8.5, respectively. In a separate test without lead, these pH values were determined to be near the lower and upper 72 hour LC50 value limits for sludge worms. The author also showed that at the optimum pH survival level of 7.5 all sludge worms lived when exposed for 24 hours to concentrations of lead ranging from 10,000 to 50,000 µg/l.

Because lead toxicity to fish was shown to be significantly related to water hardness, it was necessary to know the hardness values for as many tests as possible with invertebrate species. Hardness values (Table 2) for rotifers, Daphnia magna and isopods were reported by the authors. Cairns, et al. (1976) did not report water hardness; therefore, a value was taken from the authors' previously reported work conducted at the same laboratory. Baudouin and Scoppa (1974) also did not report water hardness; however, it was possible to calculate a hardness value by using the authors reported test water values for pH, alkalinity, calcium and conductivity. A comparison of adjusted LC50 values between fish and invertebrates species shows that except for rotifers the invertebrate species are generally more sensitive to lead than fish in either hard or soft water.

Although a wide variety of invertebrate species have been tested (Table 2), no reports were found in the literature which tested lead toxicity on the same species in both hard and soft water. However, it seems logical to assume that a similar relationship exists between acute lead toxicity and water hardness for invertebrate species as was demonstrated for acute exposures of fish. This relationship was therefore estimated for invertebrate species by using the slope (1.51) from fish acute values. Calculated logarithmic intercepts, as a measure of relative species sensitivity, ranged from -0.10 for Daphnia hyalina to 5.59 for the rotifer (Philodina acuticornis), with a geometric mean of 1.65. Following adjustment using the species sensitivity factor (21), the intercept is -1.39. This would indicate that the invertebrate species tested are slightly more sensitive to lead than fish. Thus the Final Invertebrate Acute Value is given by: $e^{(1.51 \ln(\text{hardness}) - 1.39)}$ which also becomes the equation for the Final Acute Value.

Chronic Toxicity

Chronic tests have been conducted with lead and six species of fish (Table 3). All chronic tests were conducted in soft water (33-44 mg/l as $CaCO_3$).

No acceptable hard water chronic tests were found in the literature to compare with the soft water data. Davies, et al. (1976) reported the long-term effects of lead on rainbow trout in hard and soft water (Table 7). Although these tests were neither life cycle, partial life cycle, nor embryo-larval tests, they do provide useful information. During these 19-month exposures a significant number of trout developed spinal deformities, eroded fins and blacktails in both hard (353 mg/l as $CaCO_3$) and soft (28 mg/l as $CaCO_3$) water at measured lead concentrations of 380 and 13 ug/l, respectively (Table 7). These results, therefore, established a definite relationship between water hardness and chronic lead toxicity to fish in which the rainbow trout sensitivity varied by a factor of 29 times.

Since no other appropriate fish data were available to establish a significant relationship between chronic toxicity values and hardness, a relationship was estimated by using the slope (1.51) from fish acute values. Calculated intercepts for the six species tested ranged from -1.81 for lake trout to -1.03 for white suckers, with a mean of -1.47. The adjusted mean intercept (-3.37) is below that for all species. Thus the Final Fish Chronic Value is obtained from $e^{(1.51 \ln(\text{hardness}) - 3.37)}$.

Only one invertebrate chronic test result was found in the literature (Table 4). This test with _Daphnia magna_ was conducted in soft water and the resulting chronic value was seven times lower than the acute value (Table 2) in the same water. Daphnids were among the most sensitive invertebrate species tested in the acute exposures; therefore, it would seem reasonable to assume that the chronic lead value for _Daphnia_ magna would be equal to or lower than most other invertebrate chronic values. Therefore, it would appear to be inappropriate to use the Guidelines' species sensitivity factor of 5.1 with the chronic data for _Daphnia magna_, since it is one of the most sensitive invertebrate species. Consequently, that sensitivity factor will not be used in the calculations to derive the Final Invertebrate Chronic Value. It is also interesting to note that the _Daphnia magna_ chronic value for lead is very close to the fish chronic values (Table 3). Even though invertebrate chronic tests have not been conducted in hard water it would again seem logical to assume that a similar relationship probably exisits between chronic lead toxicity and water hardness for invertebrate species as was demonstrated for acute and chronic exposures of fish (Tables 1 and 7).

Since appropriate invertebrate data were not available to establish a relationship between chronic toxicity values and hardness, a relationship was estimated by using the slope (1.51) from fish acute values and the lead value and water hardness from the _Daphnia magna_ chronic test. Thus the Final Invertebrate Chronic Value is obtained from $e^{1.51 \ln(\text{hardness}) - 1.75)}$.

Since the Final Fish Chronic Value is lower than that for invertebrate species, it is used to establish the 24-hour average lead concentrations for the protection of freshwater organisms in waters of various hardness.

Plant Effects

Fifteen tests on eight different species of aquatic plants were found in the literature and are shown in Table 5. Plant exposures by Malanchuk and Gruendling (1973) and Monahan (1976) were conducted for 24 hours and 7 days, respectively. All tests were static and all concentrations unmeasured. The lowest lead value for these plants (500 µg/l) was established as the Final Plant Value and is well above the 24-hour average lead concentrations.

Residues

Table 6 contains equilibrium bioconcentration factors for lead for two fish species. The bioconcentration factor for brook trout was calculated from a laboratory exposure by Holcombe, et al. (1976) which included 20 measurements of lead concentrations in the water during the 140-day test. Lead residues reported by Atchison, et al. (1977) were obtained from a mixed population of bluegills collected from a small 300-acre lake. The average concentration for lead in water for this contaminated lake was determined from 36 separate measurements. Since no maximum permissible tissue concentration is available for lead, no Residue Limited Toxicant Concentration can be calculated.

Miscellaneous

Table 7 contains no data that would appear to alter the 24-hour average lead concentrations.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

Final Fish Acute Value = $e^{(1.51 \ln(\text{hardness}) + 2.50)}$

Final Invertebrate Acute Value = $e^{(1.51 \ln(\text{hardness})-1.39)}$

Final Acute Value = $e^{1.51 \ln(\text{hardness}) - 1.39)}$

Final Fish Chronic Value = $e^{(1.51 \ln(\text{hardness}) - 3.37)}$

Final Invertebrate Chronic Value = $e^{(1.51 \ln(\text{hardness})-1.75)}$

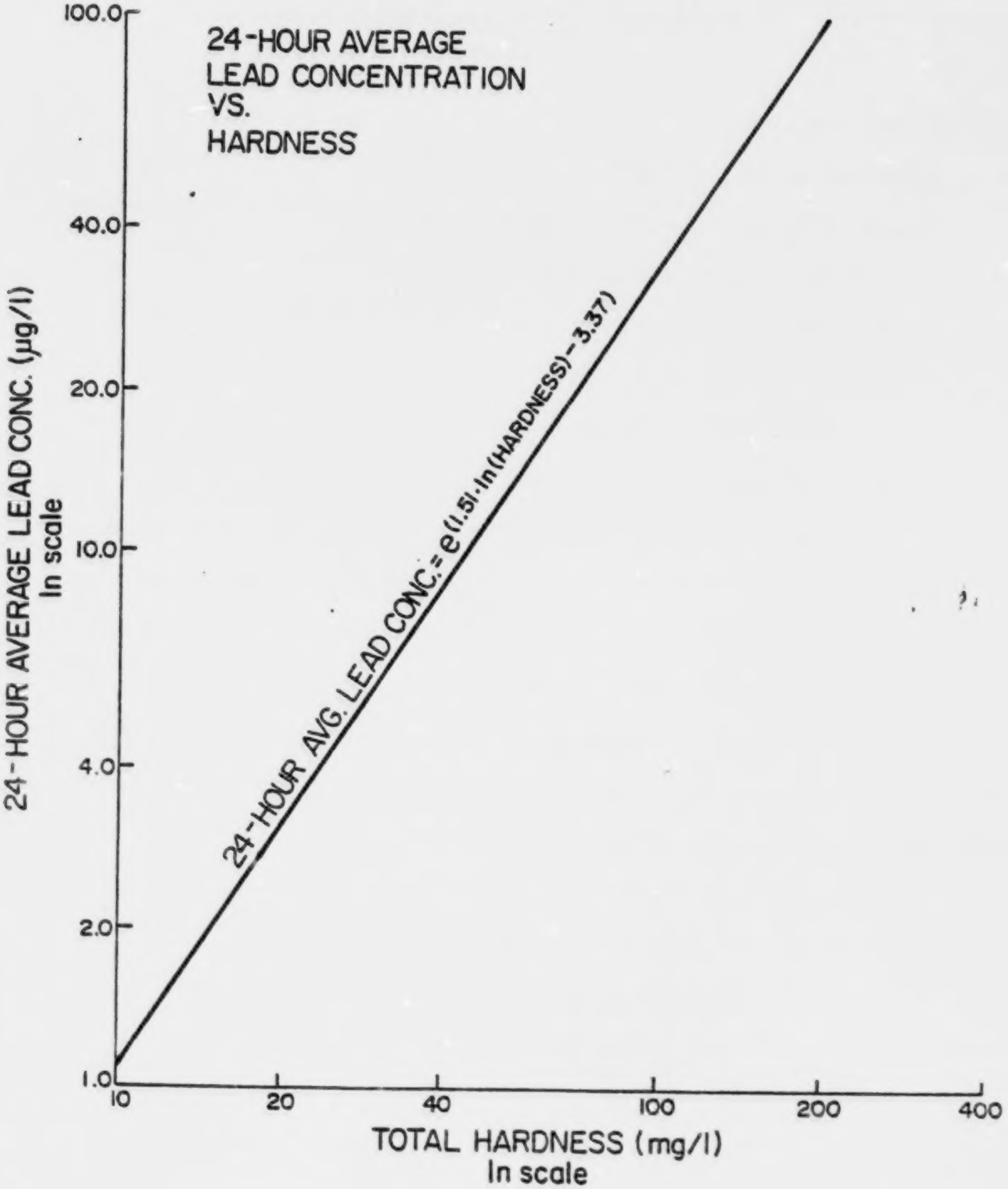
Final Chronic Value = $e^{(1.51 \ln(\text{hardness}) - 3.37)}$

Final Plant Value = 500 µg/l

Residue Limited Toxicant Concentration = not available

The maximum concentration of lead is the Final Acute Value of $e^{(1.51 \ln(\text{hardness}) - 1.39)}$ and the 24-hour average concentration is the Final Chronic Value of $e^{(1.51 \ln(\text{hardness}) 3.37)}$. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For lead the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(1.51 \ln)-}$ (hardness) - 3.37" as a 24-hour average (see the figure "24-hour average lead concentration vs. hardness") and the concentration should not exceed "$e^{(1.51 \ln(\text{hardness}) - 1.39)}$" (see the figure "maximum lead concentration vs. hardness") at any time.


24-HOUR AVERAGE
LEAD CONCENTRATION
VS.
HARDNESS
24-HOUR AVERAGE LEAD CONC. (μg/l)
ln scale
100.0
40.0
20.0
10.0
4.0
2.0
1.0
24-HOUR AVG. LEAD CONC.= e(1.51·ln(HARDNESS)−3.37)
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

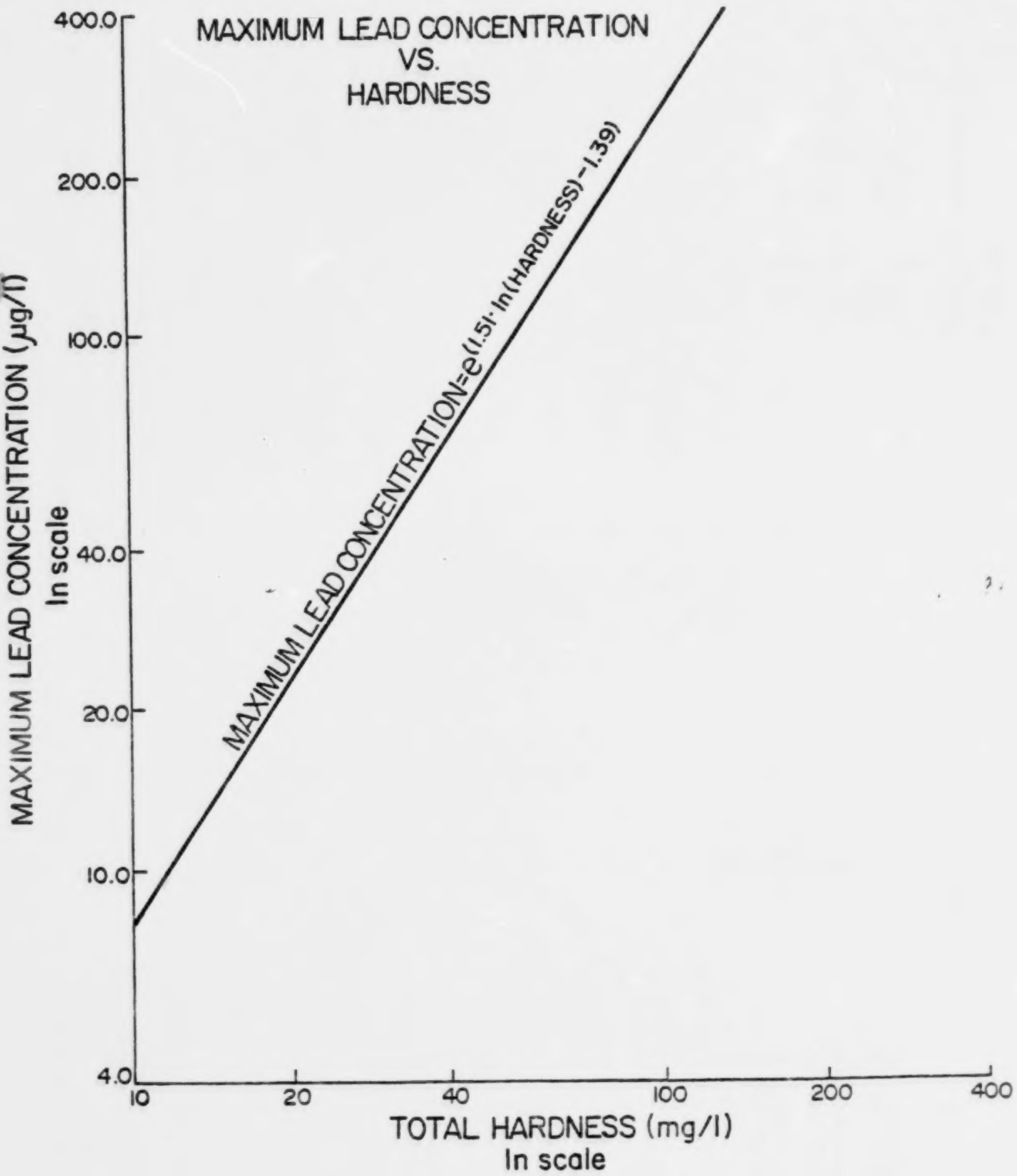

MAXIMUM LEAD CONCENTRATION
VS.
HARDNESS
MAXIMUM LEAD CONCENTRATION=e^(1.51·ln(HARDNESS)-1.39)
400.0
200.0
100.0
40.0
20.0
10.0
4.0
MAXIMUM LEAD CONCENTRATION (μg/l)
ln scale
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

Table 1. Freshwater fish acute values for lead

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	S	U	353	96	507,000	277,177	Davies, et al. 1976
Rainbow trout, Salmo gairdneri	FT	M	28	96	1,170	1,170	Davies, et al. 1976
Rainbow trout (2 mos), Salmo gairdneri	FT	U	-	96	8,000	6,160	Hale, 1977
Brook trout (18 mos), Salvelinus fontinalis	FT	M	44	96	4,100	4,100	Holcombe, et al. 1976
Red shiner, Notropis lutrensis	S	U	-	48	630,000	278,981	Wallen, et al. 1957
Fathead minnow, Pimephales promelas	S	U	20	96	2,400	1,312	Tarzwell & Henderson, 1960
Fathead minnow, Pimephales promelas	S	U	20	96	5,580	3,051	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	20	96	7,330	4,007	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	20	96	7,480	4,089	Pickering & Henderson, 1966
Fathead minnow, Pimephales promelas	S	U	360	96	482,000	263,509	Pickering & Henderson, 1966
Goldfish, Carassius auratus	S	U	20	96	31,500	17,221	Pickering & Henderson, 1966
Mosquitofish (adult), Gambusia affinis	S	U	-	96	240,000	131,208	Wallen, et al. 1957
Guppy (6 mos), Poecilia reticulata	S	U	20	96	20,600	11,262	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	20	96	23,800	13,012	Pickering & Henderson, 1966
Bluegill, Lepomis macrochirus	S	U	360	96	442,000	241,641	Pickering & Henderson, 1966

Table 1. (Continued)

Species	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference

* S = static, FT = flow through

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

Rainbow trout: slope = 2.16, intercept = - 0.12, r = 1.0, Not significant, N = 2

Fathead minnow: slope = 1.57, intercept = 3.26, r = 0.97, p = 0.01, N = 5

Bluegill: slope = 1.01, intercept = 6.45, r = 1.0, Not significant, N = 2

Geometric mean slope = 1.51

Mean intercept for 6 species = 3.86

Adjusted mean intercept = 3.86 - ln(3.9) = 2.50

Final Fish Acute Value = $e^{(1.51 \cdot \ln(\text{hardness}) + 2.50)}$

Table 2. Freshwater invertebrate acute values for lead

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rotifer, *Philodina acuticornis*	S	U	25	96	40,800	34,558	Buikema, et al. 1974
Sludge worm, *Tubifex sp.*	S	U	-	24	49,000	10,791	Whitley, 1968
Sludge worm, *Tubifex sp.*	S	U	-	24	27,500	6,056	Whitley, 1968
Snail, *Goniobasis livescens*	S	U	154	48	71,000	25,859	Cairns, et al. 1976
Snail, *Lymnaea emarginata*	S	U	154	48	14,000	5,099	Cairns, et al. 1976
Cladoceran, *Daphnia magna*	S	U	43	48	450	382	Biesinger & Christensen, 1972
Cladoceran, *Daphnia hyalina*	S	U	66	48	600	508	Baudouin & Scoppa, 1974
Copepod, *Cyclops abyssorum*	S	U	66	48	5,500	4,659	Baudouin & Scoppa, 1974
Copepod, *Eudiaptomus padanus*	S	U	66	48	4,000	3,388	Baudouin & Scoppa, 1974
Isopod, *Asellus meridianus*	R	M	25	48	280	132	Brown, 1976

* S = static, R = renewal

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness:

No hardness relationship could be derived for any invertebrate species

Using the geometric mean slope from the Fish Acute Value , the geometric mean intercept for 8 invertebrate species = 1.65

Adjusted mean intercept = 1.65 -ln(21) = - 1.39

Final Invertebrate Acute Value = $e^{(1.51 \cdot \ln(\text{hardness}) - 1.39)}$

Table 3. Freshwater fish chronic values for lead

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Rainbow trout Salmo gairdneri	E-L	71-146	51	35	Sauter, et al. 1976
Brook trout, Salvelinus fontinalis	LC	58-119	83	44	Holcombe, et al. 1976
Lake trout, Salvelinus namaycush	E-L	48-83	32	33	Sauter, et al. 1976
Channel catfish, Ictalurus punctatus	E-L	75-136	51	36	Sauter, et al. 1976
White sucker, Catostomus commersoni	E-L	119-253	87	38	Sauter, et al. 1976
Bluegill, Lepomis macrochirus	E-L	70-120	46	41	Sauter, et al. 1976

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* E-L = embryo-larval, LC = life cycle or partial life cycle

Fish Chronic Value vs. hardness:

No hardness relationship could be derived for any fish species

Slope = 1.51 from Fish Acute Value

Geometric mean intercept for 6 species = - 1.47

Adjusted mean intercept = -1.47- ln(6.7) = - 3.37

Final Fish Chronic Value = $e^{(1.51 \cdot \ln(\text{hardness}) - 3.37)}$

Application Factor Values**

Species	96-hr LC50 (µg/l)	MATC (µg/l)	AF	Reference
Brook trout, Salvelinus fontinalis	4,100	58-119	0.02	Holcombe, et al. 1976

Geometric mean AF = 0.02

** The Final Fish Chronic Value is below the chronic value derived using the application factor

Table 4. Freshwater invertebrate chronic values for lead (Biesinger & Christensen, 1972)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)
Cladoceran, *Daphnia magna*	LC	30-100	55	45

* LC = life cycle or partial life cycle

Invertebrate Chronic Value vs. hardness:

No hardness relationship could be derived for any invertebrate species.

Slope = 1.51 from fish acute value

Intercept for *Daphnia* = - 1.75 (only species tested)

Final Invertebrate Chronic Value = $e^{(1.51 \cdot \ln(\text{hardness}) - 1.75)}$

Table 5. Freshwater plant effects for lead

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Anabaena sp.*	50% reduction of $^{14}CO_2$ fixation	15,000	Malanchuk & Gruendling, 1973
Alga, *Anabaena sp.*	50% reduction of $^{14}CO_2$ fixation	26,000	Malanchuk & Gruendling, 1973
Alga, *Anabaena sp.*	50% reduction of $^{14}CO_2$ fixation	15,000	Malanchuk & Gruendling, 1973
Alga, *Ankistrodesmus sp.*	24% growth inhibition	1,000	Monahan, 1976
Alga, *Chlamydomonas sp.*	50% reduction of $^{14}CO_2$ fixation	17,000	Malanchuk & Gruendling, 1973
Alga, *Chlamydomonas sp.*	50% reduction of $^{14}CO_2$ fixation	17,000	Malanchuk & Gruendling, 1973
Alga, *Chlorella sp.*	53% growth inhibition	500	Monahan, 1976
Desmid, *Cosmarium sp.*	50% reduction of $^{14}CO_2$ fixation	5,000	Malanchuk & Gruendling, 1973
Desmid, *Cosmarium sp.*	50% reduction of $^{14}CO_2$ fixation	5,000	Malanchuk & Gruendling, 1973
Desmid, *Cosmarium sp.*	50% reduction of $^{14}CO_2$ fixation	5,000	Malanchuk & Gruendling, 1973
Diatom, *Navicula sp.*	50% reduction of $^{14}CO_2$ fixation	17,000	Malanchuk & Gruendling, 1973
Diatom, *Navicula sp.*	50% reduction of $^{14}CO_2$ fixation	28,000	Malanchuk & Gruendling, 1973
Diatom, *Navicula sp.*	50% reduction of $^{14}CO_2$ fixation	17,000	Malanchuk & Gruendling, 1973
Alga, *Scenedesmus sp.*	35% growth inhibition	500	Monahan, 1976
Alga, *Selenastrum sp.*	52% growth inhibition	500	Monahan, 1976

Final Plant Value = 500 µg/l

Table 6. Freshwater residues for lead

Organism	Bioconcentration Factor*	TIME (days)	Reference
Brook trout (embryo-3 mos), *Salvelinus fontinalis*	42	140	Holcombe, et al. 1976
Bluegill, *Lepomis macrochirus*	45	-	Atchison, et al. 1977

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* Bioconcentration factors have been converted from dry weight to wet weight.

Geometric mean bioconcentration factor for all species = 43.

Table 7. Other freshwater data for lead

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (µg/l)	Reference
Cladoceran, Daphnia magna	21 days	LC50	43	300	Biesinger & Christensen, 1972
Isopod, Asellus meridianus	20 days	Reduced growth	25	100	Brown, 1976
Mayfly, Ephemerella grandis	14 days	LC50	50	3,500	Nehring, 1976
Mayfly (nymph), Ephemerella grandis	14 days	Bioconcentration factor = 2,366	50	-	Nehring, 1976
Mayfly, Ephemerella subraria	7 days	LC50	44	16,000	Warnick & Bell, 1969
Stonefly, Pteronarcys californica	14 days	Bioconcentration factor = 86	50	-	Nehring, 1976
Caddisfly, Hydropsyche betteni	7 days	LC50	44	32,000	Warnick & Bell, 1969
Frog (adult), Rana pipiens	30 days	Death	-	100	Kaplan, et al. 1967
Rainbow trout, Salmo gairdneri	28 days	Inhibition of ALA-D activity	135	13	Hodson, 1976
Rainbow trout (12 mos), Salmo gairdneri	14 days	Inhibition of ALA-D activity	135	10	Hodson, et al. 1977
Rainbow trout, Salmo gairdneri	19 mos	Lordoscoliosis, eroded fins, black tail	353	380	Davies, et al. 1976
Rainbow trout, Salmo gairdneri	19 mos	Lordoscoliosis, eroded fins, black tail	28	13	Davies, et al. 1976
Brook trout, Salvelinus fontinalis	21 days	Stamina	-	14	Adams, 1975
Brook trout (12 mos), Salvelinus fontinalis	14 days	Inhibition of ALA-D activity	135	90	Hodson, et al. 1977

Table 7. (continued)

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (µg/l)	Reference
Brook trout (embryo-21 day), *Salvelinus fontinalis*	38 days	Elevation of ALP and ACH activity	44	525	Christensen, 1975
Brook trout (12 mos), *Salvelinus fontinalis*	56 days	Decrease of hemoglobin and inhibition of GOT activity	44	58	Christensen, et al. 1977
Goldfish (<12 mos), *Carassius auratus*	14 days	Inhibition of ALA-D activity	135	470	Hodson, et al. 1977
Pumpkinseed (>12 mos), *Lepomis gibbosus*	14 days	Inhibition of ALA-D activity	135	90	Hodson, et al. 1977

SALTWATER ORGANISMS

Introduction

The data base for the effects of lead on saltwater species is quite limited when compared to that available for freshwater species. A study on the effect of lead on cholinesterase inhibition in shiner perch is the only study conducted with saltwater fish. There are limited data for shellfish and various algae but no chronic test data are available.

Acute Toxicity

The acute toxicity data base for saltwater organisms is limited to static tests with invertebrate species. The LC50 values ranged from 2,450 µg/l for oyster larvae (Calabrese, et al. 1973) to 22,869 µg/l for adults for soft shell clams (Eisler, 1977). After adjustment for testing procedures and species sensitivity according to the Guidelines, these data result in the Final Invertebrate Acute Value of 50 µg/l which becomes the Final Acute Value.

Chronic Toxicity

No life cycle or embryo-larval tests have been conducted with lead and saltwater organisms.

Bioconcentration

Traditionally, shellfish have been used in bioconcentration studies since they are known to be excellent bioconcentrators of metals. Schulz-Baldes (1972) reported that mussels (*Mytilus edulis*) could bioconcentrate lead 2,568 times that concentration found in their immediate environment (Table 9). The hard clam (*Mercenaria mercenaria*) appears to be the least efficient concentrator of lead (Table 2). It is evident in Table 2 that different bioconcentration values are obtained with the same species. This can best be explained by the fact that bioconcentration of metals by molluscs is affected seasonally, by differences in the weight of the individuals, length of exposure to the metal, water temperature, experimental design and the chemical form of the metal in salt water. Attempts to normalize the bioconcentration data according to exposure time would be futile since so many other parameters (as mentioned above) equally affect the accumulation, therefore each study has to be accepted on its own merits.

Diatoms and other phytoplankton also bioconcentrate lead (Table 9). Since these organisms serve as food for molluscs, studies have been reported whereby lead accumulation by molluscs is affected by the concentration of lead in food organisms. Schulz-Baldes (1974) showed that mussels (Mytilus edulis) took up 23.5 percent of the lead available in food organisms as compared to 29 percent of that available in the water. Abalone (Haliotus rufescens) accumulated 21 mg/kg of lead while feeding on a brown alga pretreated with lead (Stewart, et al. 1976).

According to the Guidelines a maximum permissible tissue concentration is needed to calculate a Residue Limited Toxicant Concentration (RLTC). Since none is available for lead, no RLTC can be calculated.

Miscellaneous

Studies have been reported on the sublethal effects of lead to saltwater invertebrate species, fish and plankton (Table 10). Included in these sublethal effects is reduction in growth rate and development of adult and larval forms, inhibition of enzymes and physiological processes (respiration, photosynthesis) and delayed cell division. These effects were observed in lead concentrations ranging from 14 µg/l to 60,000 ug/l. The significance of these sublethal effects has not been established for saltwater species. While these are much less subtle than death to assess survival of a population, they clearly cause stress to the individuals which increases susceptibility predation and parasitization. This can have detrimental effects on a population if the stress is allowed to continue in a natural environment.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of lead.

Final Fish Acute Value = not available

Final Invertebrate Acute Value = 50 µg/l

Final Acute Value = 50 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = 8.5 µg/l

Final Chronic Value = 8.5 µg/l

0.44 x Final Acute Value = 21 µg/l

No saltwater criterion can be derived for lead using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

CRITERION: For saltwater aquatic life, no criterion for lead can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Table 8. Marine invertebrate acute values for lead

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Polychaete (trochophore), *Capitella capitata*	S	U	96	1,200	1,016	Reish, et al. 1976
Oyster (larva), *Crassostrea virginica*	S	U	48	2,200-3,600	1,860-3,040	Calabrese, et al. 1973
Hard clam (larva), *Mercenaria mercenaria*	S	U	48	720-800	609-677 (643)	Calabrese & Nelson, 1974
Soft shell clam (adult), *Mya arenaria*	S	U	96	27,000	22,869	Eisler, 1977

* S = static

** U = unmeasured

Geometric mean of adjusted values = 2,460 µg/l $\frac{2,460}{49}$ = 50 µg/l

Table 9. Marine residues for lead

Organism	Bioconcentration Factor	Time (days)	Reference
Oyster, *Crassostrea virginica*	536	140	Zaroogian, Manuscript
Oyster, *Crassostrea virginica*	68*	49	Pringle, et al. 1968
Oyster, *Crassostrea virginica*	1,400	70	Shuster & Pringle, 1969
Quahaug, hard clam, *Mercenaria mercenaria*	17.5*	56	Pringle, et al. 1968
Soft shell clam, *Mya arenaria*.	112*	70	Pringle, et al. 1968
Mussel, *Mytilus edulis*	650*	40	Schulz-Baldez, 1974
Mussel, *Mytilus edulis*	200*	37	Talbot, et al. 1976
Mussel, *Mytilus edulis*	2,568*	130	Schulz-Baldes, 1972
Mussel, *Mytilus edulis*	2,077*	130	Schulz-Baldes, 1972
Mussel, *Mytilus edulis*	796*	130	Schulz-Baldes, 1972
Diatom, *Phaeodactylum tricornutum*	1,050*	1/24	Schulz-Baldes, 1976
Phytoplankton, *Platymonas subcordiformis*	933*	1/24	Schulz-Baldes, 1976

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* Dry weight to wet weight conversion

Geometric mean bioconcentration factor for all species = 293

Table 10. Other marine data for lead

Organism	Test Duration	Effect	Result (µg/l)	Reference
Ciliate protozoan, Cristigera sp.	12 hrs	Reduced growth rate by 8.5%	150	Gray & Ventilla, 1973
Ciliate protozoan, Cristigera sp.	12 hrs	Reduced growth rate by 11.7%	300	Gray & Ventilla, 1973
Polychaete, Ophryotrocha labronica	>600 hrs	LC50	1,000	Brown & Ahsanullah, 1971
Oyster, Crassostrea virginica	1 yr	Oysters accumulated 0.88 µg/g wet wt. Sea H_2O sampled monthly no lead added (BCF = 326)	-	Kopfler & Mayer, 1973
Abalone, Haliotus rufescens	6 mos	Accumulated 21 µg/g wet wt while being fed a brown alga (Egregia laevigata) which was pretreated with 1 mg Pb/l.		Steward & Schulz-Baldes, 1976
Soft shell clam, Mya arenaria	168 hrs	LC50	8,800	Eisler, 1977
Mussel, Mytilis edulis	40 days	LC50	30,000	Talbot, et al. 1976
Mussel, Mytilus edulis	150 hrs	LT50 for adults	500	Schulz-Baldes, 1972
Mud crab, Rhithropanopeus harisii	--	Delayed larval development	50	Benjyts-Claus & Benijts, 1975
Fiddler crab, Uca pugilator	2 wks	Accumulated 2.04 µg Pb/g wet wt (BCF = 20)	100	Weis, 1976

Table 10. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Sea urchin, *Arbacia punctulata*	--	Few gastrula developed	14	Waterman, 1937
Shiner perch, *Cymatogaster aggregata*	--	27% inhibition of brain cholinesterase	7.8	Abou-Donia & Menzel, 1967
Alga, *Laminaria digitata*	30-31 days	50-60% reduction in growth	1,000	Bryan, 1976
Diatom, *Phaeodactylum tricornutum*	24 hrs	Completely inhibited photosynthesis	10,000	Woolery & Lewin, 1976
Diatom, *Phaeodactylum tricornutum*	48-72 hrs	Reduced photosynthesis and respiration by 25-50%	100	Woolery & Lewin, 1976
Diatom, *Phaeodactylum tricornutum*	72 hrs	No growth inhibition	1,000	Hannan & Patouillet, 1972
Phytoplankton, *Platymonas subcordiformis*	--	Retarded population grow growth by delaying cell division	2,500	Hessler, 1974
Phytoplankton, *Platymonas subcordiformis*	--	Caused inhibition of growth and death occurred	60,000	Hessler, 1974
Phytoplankton, *Platymonas subcordiformis*	2 days	48% of cells in culture died	2,500	Hessler, 1975
Phytoplankton, *Platymonas subcordiformis*	6 days	98% of cells in culture died	60,000	Hessler, 1975

REFERENCES

Abou-Donia, M.B., and D.B. Menzel. 1967. Fish brain cholinesterase: Its inhibition by carbamates and automatic assay. Comp. Biochem. Physiol. 21: 99.

Adams, E.S. 1975. Effect of lead and hydrocarbons from snowmobile exhaust on brook trout (Salvelinus fontinalis). Trans. Am. Fish. Soc. 104: 363.

Atchison, G.J., et al. 1977. Trace metal contamination of bluegill (Lepomis macrochirus) from two Indiana lakes. Trans. Am. Fish. Soc. 106: 637.

Baudouin, M.F., and P. Scoppa. 1974. Acute toxicity of various metals to freshwater zooplankton. Bull. Environ. Contam. Toxicol. 12: 745.

Benijts-Claus, C., and F. Benijts. 1975. Pages 43-52. In J.H. Koeman, and J.J. Strik, eds. Sublethal effects of toxic chemicals on aquatic animals. Elsevier Publ. Co., Amsterdam.

Biesinger, K.E., and G.M. Christensen. 1972. Effect of various metals on survival, growth, reproduction and metabolism of Daphnia magna. Jour. Fish. Res. Board Can. 29: 1691.

Brown, B.E. 1976. Observations on the tolerance of the isopod Asellus meridianus rac. to copper and lead. Water Res. 10: 555.

Brown, B., and M. Ahsanullah. 1971. Effect of heavy metals on mortality and growth. Mar. Pollut. Bull. 2: 182.

Bryan, G.W. 1976. Heavy metal contamination in the sea. Pages 185-302 *in* R. Johnston, ed. Marine . pollution. Academic Press.

Buikema, A.L., et al. 1974. Evaluation of *Philodina acuticornis* (Rotifera) as a bioassay organism for heavy metals. Water Resour. Bull. 10: 648.

Cairns, J., et al. 1976. Invertebrate response to thermal shock following exposure to acutely sub-lethal concentrations of chemicals. Arch. Hydrobiol. 77: 164.

Calabrese, A., and D.A. Nelson. 1974. Inhibition of embryonic development of the hard clam, *Mercenaria mercenaria*, by heavy metals. Bull. Environ. Contam. Toxicol. 11: 92.

Calabrese, A., et al. 1973. The toxicity of heavy metals to embryos of the American oyster *Crassostrea virginica*. Mar. Biol. 18: 162.

Christensen, G.M. 1975. Biochemical effects of methylmercuric chloride, cadmium chloride and lead nitrate on embryos and alevins of the brook trout. Toxicol. Appl. Pharmacol. 32: 191.

Christensen, G., et al. 1977. The effect of methylmercuric chloride, cadmium chloride and lead nitrate on six biochemical factors of the brook trout (Salvelinus fontinalis). Toxicol. Appl. Pharmacol. 42: 523.

Davies, P.H., et al. 1976. Acute and chronic toxicity of lead to rainbow trout (Salmo gairdneri) in hard and soft water. Water Res. 10: 199.

Eisler, R. 1977. Acute toxicities of selected heavy metals to the softshell clam, Mya arenaria. Bull. Environ. Contam. Toxicol. 17: 137.

Gray, J.S., and R.J. Ventilla. 1973. Growth rates of sediment-living marine protozoan as a toxicity indicator for heavy metals. Ambio. 2: 118.

Hale, J.G. 1977. Toxicity of metal mining wastes. Bull. Environ. Contam. Toxicol. 17: 66.

Hannan, P.J., and C. Patouillet. 1972. Effect of mercury on algal growth rates. Biotech. Bioen. 14: 93.

Hessler, A. 1974. Effects of lead on algae. I. Effects of Pb on viability and motility of Platymonas subcordiformis (Chlorophyta:volvocales). Water Air Soil Pollut. 3: 371.

Hessler, A. 1975. Effects of lead on algae. Mutagenesis experiments on Platymonas subcordiformis (Chlorophyta:valvocales). Mutat. Res. 31: 43.

Hodson, P.V. 1977. Amion levulinic acid dehydratase activity of fish blood as indicator of harmful exposure to lead. Jour. Fish. Res. Board Can. 33: 268.

Hodson, P.V., et al. 1977. Evaluation of erythrocyteamion levulinic acid dehydratase activity as a short-term indicator in fish of a harmful exposure to lead. Jour. Fish. Res. Board Can. 34: 501.

Holcombe, G.W., et al. 1976. Long term effects of lead exposure on three generations of brook trout (Salvelinus fontinalis). Jour. Fish. Res. Board Can. 33: 1731.

Kaplan, H.M., et al. 1967. Toxicity of lead nitrate solutions for frogs (Rana pipins). Lab. Anim. Care 17: 240.

Kopfler, F.C., and J. Mayer. 1973. Concentration of five trace metals in the waters and oysters (Crassostrea virginica) of Mobile Bay, Alabama. Proc. Natl. Shellfish Assoc. 63: 27.

Malanchuk, J.L., and G.K. Gruendling. 1973. Toxicity of lead nitrate to algae. Water Air and Soil Pollut. 2: 181.

Monahan, T.J. 1976. Lead inhibition of chlorophycean microalgae. Jour. Psycol. 12: 358.

Nehring, R.B. 1976. Aquatic insects as biological monitors of heavy metal pollution. Bull. Environ. Contam. Toxicol. 15: 147.

Pickering, Q.H., and C. Henderson. 1966. The acute toxicity of some heavy metals to different species of warmwater fishes. Air Water. Pollut. Int. Jour. 10: 453.

Pringle, B.H., et al. 1968. Trace metal accumulation by estuarine mollusks. Proc. Am. Soc. Civil. Eng., Jour. San. Eng. Div. SA3, 455-475.

Reish, D.J., et al. 1976. The effect of heavy metals on laboratory populations of two polychaetes with comparisons to the water quality conditions and standards in Southern California marine waters. Water Res. 10: 299.

Sauter, S., et al. 1976. Effects of exposure to heavy metals on selected freshwater fish. Ecol. Res. Ser. EPA 600/3-76-105.

Schulz-Baldes, M. 1972. Toxizitat und anreicherung von Blei bei der Miesmuschel Mytilis edulis im Laborexperiment. Mar. Biol. 16: 266.

Schulz-Baldes, M. 1974. Lead uptake from seawater and food, and lead loss in the common mussel Mytilis edulis. Mar. Biol. 25: 177.

Schulz-Baldes, M. 1976. Lead uptake in two marine phytoplankton organisms. Biol. Bull. 150: 118.

Shuster, C.N., and B.H. Pringle. 1969. Trace metal accumulation by the American Eastern oyster, Crassostrea virginica. Proc. Natl. Shellfish Assoc. 59: 91.

Stewart, J., and M. Schulz-Baldes. 1976. Long-term lead accumulation in Abalone (Haliotus sp.) fed on lead-treated brown algae (Egregia laevigata). Mar. Biol. 36: 19.

Talbot, V., et al. 1976. Lead in Port Phillip Bay mussels. Mar. Pollut. Bull. 7: 234.

Tarzwell, C.M., and C. Henderson. 1960. Toxicity of less common metals to fishes. Ind. Wastes 5: 12.

Wallen, I.E., et al. 1957. Toxicity to Gambusia affinis of certain pure chemicals in turbid waters. Sewage Ind. Wastes 29: 695.

Warnick, S.L., and H.L. Bell. 1969. The acute toxicity of some heavy metals to different species of aquatic insects. Jour. Water Pollut. Control Fed. 41: 280.

Waterman, A.J. 1937. Effects of salts of heavy metals on development of the sea urchin, Arbacia punctulata. Biol. Bull. 73: 401.

Weis, J.S. 1976. Effects of mercury, cadmium and lead salts on regeneration and ecdysis in the fiddler crab, Uca pugilator. U.S. Dep. Comm. Natl. Ocean. Atmos. Admin. Fish. Bull. 74: 464.

Whitley, L.S. 1968. The resistance of tubificid worms to three common pollutants. Hydrobiologia 32: 193.

Woolery, M.L., and R.A. Lewin. 1976. The effects of lead on algae. IV. Effects of lead on respiration and photosynthesis of Phaeodactylum tricornutum (Bacillariophyceae). Water Air and Soil Pollut. 6: 25.

Zaroogian, G.E. U.S. Environ. Prot. Agency Environ. Res. Lab. Narragansett, R.I. (Manuscript).

Mammalian Toxicology and Human Health Effects

Introduction

The hazards of lead exposure have been under intensive investigation for many years. Research activities continue unabated for several reasons. First, industrial production and commercial use continues at a fairly steady rate. Second, hazardous sources persist in the environment long after the hazard-generating practice has been curtailed. A good example is the persistence of lead-base paint in houses long after the elimination of lead-containing pigments from new household paints. Finally, as biomedical science in general and toxicology in particular continue to push back the frontiers of knowledge, indices of toxicity change, generally with a consequent downward revision of what is considered an acceptable level of human exposure to environmental pollutants.

Reassessment of acceptable levels of lead exposure have been fairly numerous in recent years. These have taken the form of criteria documents and of more academically-oriented reviews. Some have been highly comprehensive, covering effects on the ecosystem in general, as well as on man (Natl. Acad. Sci/Natl. Res. Counc., 1972a; Boggess, 1978). Others have been mainly concerned with effects of lead on man (World Health Organ., 1977; U.S. EPA, 1977a; Hammond, 1977a).

The purpose of this review is to summarize the literature which is most relevant to the question of what is an acceptable level of human exposure to lead via water. In doing so, it is necessary to consider the consequences to human health of one or another level of intake assignable to water and to the numerous other sources.

EXPOSURE

Natural Background Levels

Lead is ubiquitous in nature, being a natural constituent of the earth's crust. The usual concentration in rocks and in soils from natural sources ranges from 10 to 30 mg/kg. Most natural groundwaters have concentrations ranging from 1 to 10 µg/l. This is well below the United States' drinking water standard of 50 µg/l. It is much easier to specify natural levels of lead in rocks and soil than in vegetation since long-range transport of lead from man-made sources via the air inevitably contaminates both surface soil and plants growing thereon. The normal concentration of lead in rural vegetation, however, range from 0.1 to 1.0 mg/kg dry weight, or 2 to 20 mg/kg ash weight. Thus, nutrient movement from soil to the organic matter in plants via water does not result in any noticeable degree of biomagnification. Again, because of the impact of long-range transport of lead via air from man-generated sources, it is only possible to specify lowest concentrations found over areas of the globe most remote from human activity. These are of the order of 0.0001 to 0.001 $\mu g/m^3$, mostly measured over Greenland and over remote oceans.

Areas of abnormally high concentrations of lead occur in natural ores, usually in conjunction with high concentrations of cadmium and zinc. There is essentially no transfer from natural ore beds into overlying streams. There is none if the soil is even slightly alkaline (Jennett, et al. 1978).

Man-generated Sources of Lead

Lead consumption in the United States has been fairly stable from year to year at about 1.3 x 10^6 metric tons. Approximately half of that consumption has been for the manufacture of storage batteries and one-fifth has been for the manufacture of gasoline antiknock additives, notably tetraethyl- and tetramethyllead. Pigments and ceramics account for about 6 percent of annual production. All other major uses are for metallic lead products or for lead-containing alloys. The consumption of tetraethyl- and tetramethyllead are declining. Other uses that have significant potential for input into man are for paint pigment and solder. Paints applied to surfaces will eventually crack, flake or peel. Children are known to ingest this type of deteriorating paint. Solder also is a potential source of lead exposure either when used to seal water pipe joints or for joining seams in metal food and beverage containers.

Ingestion from Water

Lead does not move readily through stream beds because it easily forms insoluble lead sulfate and carbonate. Moreover, it binds avidly to organic ligands of the dead and living flora and fauna of stream beds. Nonetheless, under special circumstances, lead does have considerable potential for hazardous movement into man via drinking water. In areas where the home water supply is stored in lead-lined tanks or where it is conveyed to the water tap by lead pipes, the concentration may reach several hundred micrograms per liter or even in excess of 1000 µg/l (Beattie, et al. 1972a). There is a definite positive correlation between the concentration of lead in the domestic water supply and the concentration of lead in the blood. The concentration of lead in the water conveyed through lead pipes is dependent on a number of factors. The longer the water has stood in the pipes, the higher the lead concentration (Wong and Berrang, 1976). The lower the pH of the water and the lower the concentration of dissolved salts in the water, the greater the solubility of lead in the water. Leaching of lead from plastic pipes has also been documented (Heusgem and De Graeve, 1973). The source of lead was probably lead stearate, which is used as a stabilizer in the manufacture of polyvinyl plastics. The magnitude of the problem of excessive lead in tap water is not adequately known. In one recent survey of 969 water systems, 1.4 percent of all tap water exceeded the 50 µg/l standard (McCabe, 1970). Special attention should be given in water quality surveillance to soft water supplies, especially those on the acid side of pH 6.5. Future survey work should also indicate whether or not the water was filtered before analysis. This appears to be a common practice among water analysts. Since a substantial fraction of the lead in drinking water probably is in particulate form, filtration prior to analysis could give deceivingly low analytical values especially if a substantial fraction of the particulate lead in water is available for absorption. However, "drinking water" analyses are usually performed in unfiltered water and hence represent total lead.

Ingestion from Food

It is generally held that food constitutes the major source of lead ingested by people. Raw fruits and vegetables acquire lead by surface deposition from rainfall, dust and soil, as well as from uptake via the root system. The relative contribution of these two sources varies greatly depending upon whether the edible portion is leafy or not. Furthermore, the nature of food processing may either lower or raise the concentration in the raw product - e.g., washing as compared to packing in metal cans with lead solder seams. There is no evidence of biomagnification in the food chain, e.g., from aquatic vegetation to the edible portions of fish and shellfish. Therefore, fish do not constitute an unusually significant source of lead in man's diet. There seems to be about as much variation in the concentration of lead in specific food items as there is between food items. Thus, Schroeder, et al. (1961) reported 0 to 1.5 mg/kg of lead for condiments, 0.2 to 2.5 mg/kg for fish and seafood, 0 to 0.37 mg/kg for meat and eggs, and 0 to 1.3 mg/kg for vegetables. Other more recent studies have confirmed this observation. Many foods and beverages are packed in metal cans which have a lead-soldered side seam and caps. The concentration of lead in the contents is substantially higher than in the filler before packing, or in the same item packed in glass (Mitchell and Aldous, 1974; U.S. Food and Drug Administration, 1975). In some instances, the lead probably leaches from the solder through cracks or pores in the protective shellac coating applied to the inside of the can. In many other instances, however, microscopic pellets of lead splatter inside the can during the soldering process. Their availability for absorption may differ substantially from that of lead leached into solution.

Milk has been studied extensively as to lead content because it constitutes a substantial fraction of the diet of infants and young children. Whole raw cow milk has a concentration of about 9 µg/l (Hammond and Aronson, 1964) whereas market milk has an average of 40 µg/l (Mitchell and Aldous, 1974). Evaporated milk has been variously reported to contain an average of 202 µg/l (Mitchell and Aldous), 110 ± 11 µg/l (Lamm and Rosen, 1974), and 330 to 870 µg/l (Murthy and Rhea, 1971).

The daily dietary intake of lead has been estimated by numerous investigators, using either the duplicate portions approach or the composites technique wherein theoretical diets are derived using nutrition tables. The results are generally consistent, considering variations in body size and metabolic rates. Thus, Nordman (1975) reported an average daily intake of 231 µg Pb for Finnish adult males and 174 µg Pb for adult females. This is consistent with a British study reporting 274 µg Pb/day for young adults (Thompson, 1971) and with a Japanese study reporting 299 µg Pb/day for adult males doing medium work (Horiuchi, et al. 1956). The first two studies described above used the duplicate portions technique whereas the third used the composites approach. The one duplicate portions study is consistent with the studies cited above. Kehoe (1961) reported an average intake of 218 µg Pb/day for sedentary men. This is not consistent, however, with two other American studies of daily fecal lead excretion (Coulston, 1962 and Levin, 1972). From the lead balance studies of Kehoe (1961), it can be estimated that gastrointestinal absorption of lead approximates 10 percent. Making this adjustment daily lead intake from the diet based on fecal lead excretion would be 113 µg in sedentary adult males (Coulston, et al. 1962) and 119 µg in women (Tepper and Levin, 1972).

Many studies of dietary lead intake are somewhat vague as to whether water consumption was included in the estimates. Others specify "food and beverages."

The dietary intake of lead in infants and young children has not been studied as extensively as it has in adults. Using the duplicate diet approach, Alexander, et al. (1973) estimated a range of 40 to 210 µg/day of lead for children ranging in age from 3 months to 8.5 years. Horiuchi, et al. (1956) estimated 126 µg/day of lead for youngsters 10 months old. These seemingly high values compared to adults are not too surprising considering the high caloric and fluid requirements of children in proportion to their weight.

Inhalation

The third major obligatory source of lead in the general population is ambient air. A great deal of controversy has been generated regarding the contribution of air to total daily lead absorption. Unlike the situation with food and water, general ambient air lead concentrations vary greatly. In metropolitan areas average air lead concentrations of 2 $\mu g/m^3$ with excursions of 10 $\mu g/m^3$ in areas of heavy traffic or industrial point sources are not uncommon, whereas in non-urban areas average air lead concentrations usually are of the order of 0.1 $\mu g/m^3$. In addition, people are so mobile that static air sampling devices are not very useful for estimating the integrated air lead exposure of urban populations.

Dermal

Exposure of the skin to lead probably is significant only under special circumstances such as among workers in contact with lead-based gear compounds or greases, or blenders of alkyl lead full additives. It is very unlikely that the concentrations of lead in water or air are sufficient to make dermal contact a significant route of exposure.

Miscellaneous Sources

Among adults not occupationally exposed to lead there are several sources of lead which may assume clinically-significant proportions. Perhaps the most widespread serious problem is the consumption of illicitly-distilled whiskey ("moonshine") which often is heavily contaminated with lead. Many cases of frank lead poisoning have been documented. The concentration of lead in moonshine whiskey commonly exceeds 10 mg/l, or 2000 times the drinking water standard. Storage of acidic beverages in improperly glazed earthenware has caused severe, sometimes fatal poisoning in the consumer (Klein, et al. 1970; Harris and Elsea, 1967).

Occupational exposure to lead may be quite excessive. Thus, in primary lead smelters the air lead concentration may exceed 1000 $\mu g/m^3$ in certain areas of the plant. A similar situation exists in some storage battery manufacturing plants. Other hazardous occupations include welding and cutting of lead-painted metal structures, automobile radiator repair, and production of lead-base paints. In these occupations the principal hazard is generally considered to be from inhalation of lead fumes and dusts. Hand-to-mouth transfer probably also is significant.

The hazard of lead to children is of considerable concern. The number of children unduly exposed to lead from miscellaneous sources is impressive. Thus, federally assisted lead screening programs reveal that undue lead absorption (PbB $\geq$ 40 µg/dl) was found in 11.1 percent of 277,347 children screened in 1973. The percentage has fallen since then, being 6.4 percent in 1974 and 6.5 percent in 1975 (Hopkins and Houk, 1976). Even in 1976 the problem had not changed appreciably since 1974 and 1975. In that year 8.7 percent of 500,463 children screened had PbB's $\geq$ 30 µg/dl and 2.7 percent or 13,604 children had PbB's $\geq$ 50 µg/dl (Commun. Dis. Center, 1977).

It has long been held that the major source of elevated lead exposure in infants and young children is lead-base paint in the interior of home and in the soil surrounding the homes. More recently, the high lead content of soil and street dust attributable to the fallout of lead from automobile exhaust has become suspect. Thus, in the 1972 publication Airborne Lead in Perspective (Natl. Acad. Sci/Natl. Res. Counc., 1972), it is pointed out that the daily ingestion of 44 mg of street dust at 2000 µgPb/g would suffice to elevate the PbB of a young child from 20 µg/dl to 40 µg/dl. In a survey of 77 midwestern United States cities it was found that the average lead concentration in the street dust of residential areas was 1636 µg/g and that in commercial and industrial areas the average concentrations were, respectively, 2413 µg/g and 1512 µg/g (Hunt, et al. 1971). Soil along the shoulder of heavily-traveled roadways also is heavily contaminated, although most values found have been in the range of hundreds of micrograms per gram rather than thousands (see, for example, Langerwerff and Specht, 1970).

The relative contribution of soil, automotive exhaust fallout and paint to lead exposure in children remains uncertain. There is no question that children in the age range of 1 to 5 years, in which the problem of elevated PbB's exists, do indeed exhibit pica, the habit of mouthing or ingesting non-edible objects, e.g., pieces of plastic, gravel, cigarette butts, etc. (Barltrop, 1966). The habit also appears to be more prevalent among children who have elevated PbB's than among those who don't (Mooty, et al. 1975). There is strong evidence that paint is a major source of lead in children with pica. Thus, Sachs (1974) reported that 80 percent of patients seen because of evidence of excessive lead absorption had a history of eating paint or plaster. Hammond, et al. (1977) reported that among 29 children with elevated PbB's ($\geq$ 40 ug/dl) selected at random from a lead screening program, all but one came from 14 homes classified as having high hazard for lead-base paint, either exterior or interior (see Table 1). High hazard consisted of there being at least one accessible painted surface with $\geq$ 0.5 percent Pb, peeling or otherwise loose. The medium classification consisted of $\geq$ 0.5 percent Pb, but painted surface was generally tight. In this study there was found to be a highly significant correlation (p = 0.007) between paint hazard classification (low, medium, high) and fecal lead excretion, but no correlation between fecal lead excretion and traffic density in the vicinity of the home (p = 0.41). Unfortunately, the correla-

TABLE 1

Classification of Home Environments as to Lead Hazard[a]

Family	Paint Hazard[b]	Lead Concentration, % d.w.[c]			Vehicles per d. x 10^3
		Interior Dust	Exterior Dust	Soil	
A	H	-	0.45(2)	0.12(3)	2.5 - 5
B	H	20	0.11(2)	0.06(2)	30
C	H	-	-	0.07(1)	10 - 15
D	H	-	0.3(1)	0.3(2)	2.5 - 5
F	H	0.3(1)	0.7(1)	0.1(1)	=0.5
G	M	-	0.1(1)	0.2(1)	=0.5
H	H	-	4.0(1)	0.9(2)	4 - 6
J	H	-	1.9(1)	-	1 - 2
L	H	-	-	0.05(1)	2.5 - 5
M	L(I); H(E)	-	-	0.1(3)	0.5 - 1
N	H	-	-	-	1 - 2
P	M(I); H(E)	-	-	-	2.5 - 5
R	H	-	0.6(1)	0	4 - 6
S	L(I), H(E)	-	-	-	5 - 7.5

[a] Hammond, et al. 1977.

[b] H = high; M = medium; L = low; (I) = interior; (E) = exterior. Absence of (I) or (E) designation means that both conformed to the designated classification of H, M or L.

[c] Numbers in parentheses indicate number of environmental samples.

tion between traffic density and the lead content of soil and dust was not determined. Thus, the data are merely suggestive.

Ter Haar and Aronow (1974) reported that elevated lead exposure in a series of eight children hospitalized for excessive lead absorption could not be accounted for by lead from fallout of airborne combusted auto exhaust. Six of the eight children had distinctly elevated fecal lead excretion as compared to nine control children. Yet their excretion of ^{210}Pb, a marker for aerosol fallout, was no different from that of controls. However, the children admitted to this study were selected to have ingested paint. The criteria were one of all of the following: (1) X-ray showed radio opaque materials in the gut; (2) history of pica; (3) elevated PbB; and (4) x-ray showed Pb lines on the long bones.

There is other evidence, however, which suggests that dust and soil are, under some circumstances at least, significant sources of lead for infants and children and that their effect is additive to that produced by inhalation. The best evidence is provided in a study of a population of children residing in the immediate vicinity of a large secondary lead smelter near El Paso, Texas (Landrigan, et al. 1975). Sixty-nine percent of one-to-four year old children living within 1 mile of the El Paso smelter had blood lead levels greater than or equal to 40 µg/dl, the level then considered indicative of increased lead absorption. By contrast, the prevalence of blood lead levels greater than or equal to 40 µg/dl among 98 adults living in the same area was 16 percent. The geometric mean lead concentration of soil there was 1,791 ppm and that of house dust was 4,022 ppm. Lead based paint was not a problem. Therefore it seems likely that a proportion of the lead intake in the children living in El Paso was oral rather than by inhalation and that the net effect of the two routes of exposure was to place children at considerably increased risk of lead uptake than adults. The mere presence of high concentrations of lead in soil accessible to children is not enough to create a hazard. Thus, children living in British homes built on soils containing 8,000 µgPb/g showed a considerably lesser elevation of PbB than was found in the El Paso study (Barltrop, et al. 1974). This may be explained by other factors, e.g. rainfall and soil composition. El Paso, Texas, is a hot, dry, windy town whereas Britain has considerable rainfall, probably resulting in a heavy protective cover of vegetation.

Certain miscellaneous sources of lead are unique to children by virtue of the pica habit. These include colored newsprint (Joselow and Bogden, 1974) and other items to which lead-base pigment is applied.

PHARMACOKINETICS

In characterizing the accumulation of lead in the body under various circumstances of exposure, experimental animal data are useful for establishing relevant principles. The specific rates of transfer into, within, and out of the animal system cannot be relied upon, to reflect with any reliability the situation in man. Only human data will serve to indicate how much lead, in what form, and by what route will lead to the accumulation of one or another concentration of lead in specific organs and systems. This restriction has imposed severe limitations on knowledge concerning lead metabolism in man. Only certain human biological fluids and tissues are accessible for sampling, except after death. The human cadaver, in turn, has its own limitations, chiefly that the precise history of lead exposure prior to death is not known. Ante mortem studies of lead metabolism in human volunteers, on the other hand, have their own limitation. They provide a substantial amount of knowledge concerning the subject, but extrapolation of the data to the general population is hazardous. Population studies materially overcome this restriction, but at the expense of precision and detail of knowledge. By combining data from all sources, a reasonable understanding of lead metabolism does emerge, however.

In reviewing the metabolism of lead in man, it is generally assumed that all inorganic forms behave in the same manner once absorbed. There is no evidence to suggest that this assumption is erroneous.

Absorption

Gastrointestinal tract

The classic studies of lead metabolism in man, conducted by R. A. Kehoe and colleagues (Kehoe, 1961) indicate that, on the average and with considerable day-to-day excursions, approximately 8 percent of the normal dietary lead (including beverages) is absorbed. This conclusion was reached as a result of long-term balance studies in volunteers. Recent studies using the non-radioactive tracer ^{204}Pb have confirmed this conclusion (Rabinowitz, et al. 1974). It is of special significance that these same workers found that absorption of doses of lead nitrate, lead cysteine, and lead sulfide eaten after a 6-hour fast and followed by another 6-hour fast was up to 8-fold higher than when the lead was taken with meals (Wetherill, et al. 1974). This finding has been confirmed in mice using small doses of lead (3 µg/kg) but not when using large doses (2000 µg/kg) (Garber and Wei, 1974). Thus, lead in water and other beverages taken between meals may have a far greater impact on total lead absorption than lead taken with meals.

The gastrointestinal absorption of lead in young children is considerably greater than in adults. Alexander, et al. (1973) found that dietary lead absorption was approximately 50 percent in eight healthy children 3 months to 8.5 years of age. This finding has been confirmed using a larger number of subjects less than 2 years of age (Ziegler, et al. 1978). It is worth noting too that the same observation has been made using infant rats, thus suggesting a similarity in lead absorption characteristics (Forbes and Reina, 1974; Kostial, et al. 1971).

Numerous factors influence the absorption of lead from the gastrointestinal tract. Low dietary Ca and Fe and high dietary fat enhance lead absorption in experimental animals (Sobel, et al, 1938; Six and Goyer, 1970; Six and Goyer, 1972). Lead absorption has also been shown to be enhanced in experimental animals by high fat, low protein, and high protein diets, and to be decreased by high mineral diets (Barltrop and Khoo, 1975). There also has been shown to be an inverse relationship between dietary lead absorption and the calcium content of the diet of infants (Ziegler, et al. 1978). The chemical nature of the lead also has an influence on the degree of absorption. Thus, Barltrop and Meek (1975) reported that, in mature rats in an acute experiment, relative to the absorption of lead acetate, lead naphthenate, lead octoate, and lead sulfide were absorbed only two-thirds as well as lead acetate and that elemental lead particles, 180 to 250 μm, were absorbed only about 14 percent as well. Lead thallate and lead carbonate were absorbed somewhat better than lead acetate. Some attention has also been given to the availability for absorption of lead in dried paint. The absorption of lead naphthenate is reduced 50 percent (in rats) as a result of incorporation in paint films (Gage and Litchfield, 1969). Similarly, it has been found in monkeys that lead octoate in dried ground paint is absorbed only one-third as well as lead octoate not incorporated into paint (Kneip, et al. 1974).

Respiratory tract

There are serious problems in regard to assessing the absorption of lead via this route. The fractional deposition of inhaled aerosols is relatively easy to measure, even in man. The problem lies in determining the fate of the aerosol particles. To varying degrees, depending on their solubility and particle size, these particles will be absorbed from the respiratory tract into the systemic circulation or they will be transferred to the gastrointestinal tract by swallowing following either retrograde movement up the pulmonary bed or by drainage into the pharynx from the nasal passages. Unfortunately, the particle size distribution and solubility of lead aerosols varies tremendously, depending on their origin and residence time in the air. All of these difficulties have frustrated previous attempts to assess the impact of lead inhalation on the body burden of lead. It has always proved necessary to fall back on a more indirect approach to the problem, whereby the impact of air lead concentration on the blood lead concentration is measured. In order for this approach to be meaningful, certain conditions and restrictions must apply. First, a fairly large population of subjects is needed in order to overcome the background noise resulting from the variable impact of dietary lead on the subject's PbB's. Second, it is necessary to monitor the air breathed by the subjects continuously and for a substantial period of time. Third, the subjects must have been in the air environment being evaluated for at least three months in order to assure reasonable equilibration of air lead versus PbB. If all these conditions are achieved, the results are only applicable for the particular type of lead aerosol under study. Thus, it would not be reasonable to extrapolate data obtained in a population breathing city air to a population of industrial workers for whom the greatest source of input might be lead oxide fumes. Needless to say, these restrictions are so severe that very few good studies have been performed which would allow one to make a reasonable judgment concerning the *relative* importance of diet versus air as sources of lead absorption. An assessment of available information is deferred to the end of this section on lead metabolism.

Dermal

Very few studies concerning the dermal absorption of lead in man or experimental animals are available. Once again, the problem of the chemical form of lead comes into play. In an early study of dermal absorption of lead in rats it was found that tetraethyllead was absorbed to a substantially greater degree than lead arsenate, lead oleate, or lead acetate (Laug and Kunze, 1948). Differences in the degree of absorption among the oleate, arsenate, and acetate were not significant. In a more recent study, absorption of lead acetate and lead naphthenate through the intact skin was demonstrated, based on concentrations of lead attained in various organs as compared to controls (Rastogi and Clausen, 1976). There seems to be little question that lead can be absorbed through the intact skin, at least when applied in high concentrations such as were used in the Rastogi study (0.24M).

Distribution and Retention

The general features of lead distribution in the body are well-known, both from animal studies and from human autopsy data. Under circumstances of long-term exposure, approximately 95 percent of the total amount of lead in the body (body burden) is localized in the skeleton after attainment of maturity. By contrast, in children only 72 percent is in bone (Barry, 1975). The amount in bone increases with old age but the amount in most soft tissues, including the blood, attains a steady state early in adulthood (Barry, 1975; Horiuchi and Takada, 1954). Special note should be made regarding the kinetics of lead distribution with reference to the blood. When human volunteers are introduced into a new air environment containing substantially higher concentration of lead than the previous one, the concentration of lead in the blood rises rapidly and attains a new apparent steady state in about 60 to 100 days (Tola, et al. 1973; Rabinowitz, et al. 1974; Coulston, et al. 1962). This is probably only an apparent steady state rather than a true one because the kinetics of disappearance of lead from the blood differ depending upon whether the high level was maintained for months or for years. When men were placed in a high lead environment for 100 days and then returned to a low lead environment, the PbB concentration returned to the pre-exposure level with a disappearance half-time of only about 6 weeks. By contrast, the rate of PbB decrement in workers who retire from the lead trades is much longer (Haeger-Aronsen, et al. 1974; Prerovska and Teisinger, 1970). This suggests that true equilibrium between the blood compartment and bone compartment is only slowly attained under constant state exposure conditions, if it ever is within the human life span.

The distribution of lead at the organ and cellular levels has been studied extensively. In blood, lead is primarily localized in the erythrocytes. The ratio of the concentration of Pb in the cell to lead in the plasma is approximately 16:1. Lead crosses the placenta readily. The concentration of lead in the blood of the newborn is quite similar to the maternal blood concentration. Studies of the subcellular distribution of lead indicate that distribution occurs to all organelles, suggesting that all cellular functions at least have the opportunity to interact with lead.

Metabolism

Upon entry into the body, lead compounds occurring in the environment disassociate into lead. Therefore no question of metabolism of the pollutant is involved. The one exception is the family of alkyl lead compounds, principally tetramethyl- and tetraethyl lead. These are dealkylated to form trialkyl and dialkyl metabolites, which are more toxic than the tetralkyl form (Bolinowska, et al. 1967).

Excretion

The numerous studies reported in the literature concerning routes of excretion in experimental animals indicate wide interspecies differences. In most species biliary excretion predominates in comparison to urinary excretion, except in the baboon (Eisenbud and Wrenn, 1970). It also appears that urinary excretion predominates in man (Rabinowitz, et al. 1973). This conclusion, however, is based on data from one volunteer.

Contributions of Lead from Diet versus Air to PbB

Great concern has developed in recent years regarding the impact of air lead exposure on human health in the general population. Analysis of the contribution of ambient air to lead input in man has taken the form of an analysis of air lead versus PbP for reasons explained in the section on lead absorption. An analysis of all available data bearing on this question first appeared in the Environmental Health Criteria 3 Lead published by the World Health Organization (World Health Organ., 1977). A more rigorous and detailed analysis was published subsequently in Air Quality Criteria for Lead (U.S. EPA, 1977).

Most of the data bearing on the question of air lead versus PbB are deficient in one or another of two major respects. The most serious and frequent deficiency is the lack of continuous air sampling in the breathing zone of the subjects. An almost equally serious but less frequent deficiency is the lack of variation in the air lead concentration over the range of interest. This is, unfortunately, a problem seen in the clinical studies (as opposed to population studies) where the number of subjects is quite limited. Another problem, also limited to the clinical studies, is the artificial nature of the lead aerosol utilized. In spite of all these apparent limitations, calculations from the epidemiologic and laboratory data sources indicate a fairly narrow range of blood Pb to air Pb concentrations, namely 1 to 4 μg/dl for every microgram of air lead per cubic meter (μg/m^3). This blood Pb to air Pb ratio appears to be higher for children than adults.

Among all the studies, the only one that satisfied all criteria for good design was the one by Azar, et al. (1975a). It should be noted that the regression equation developed to describe the data (log PbB = 1.2557 + 0.153 (log μgPb/m^3)) has a slope of less than one. Thus, the incremental rise in PbB for each 1 μgPb/m^3 in air becomes progressively smaller. This relationship is consonant with experimental animal data showing that over a wide range of dietary lead levels the incremental rise in PbB decreases progressively proportional to the rise in dietary lead levels (Prpic-Majic, et al. 1973; Azar, et al. 1975b). It also is consonant with the World Health Organ. analysis of data on air lead exposure in a battery plant (World Health Organization, 1977).

TABLE 2

Estimated Blood Lead to Air Lead Ratios for Four Air Lead Concentrations[a]

			Ratio at air lead concentrations µg/m			
Study	Population	Sample Size	1.0	2.0	3.5	5.0
Epidemiological						
Azar[b]	Adult males	149	2.57	1.43	0.89	0.66
Tepper-Levin[c]	Adult females	1908	0.87	0.92	1.00	1.08
Nordman[c]	Adult males	536			(0.42)	
Nordman[c]	Adult females	478			(0.11)[a]	
Fugas[c]	Adults	330			(2.64)	
Johnson[c]	Adult males	64			(0.80)	
Johnson[c]	Adult females	107			(0.60)	
Tsuchiya[c]	Adult males	591			(3.84)	
Goldsmith[c]	Children males	202			(2.30)	
Goldsmith[c]	Children females	203			(1.70)	
Yankel-von Lindern[b]	Children	879	1.16	1.21	1.27	1.37
Chamberlain[d]-Williams	Adults	482			(1.10)	
Daines[c]	Black females	(unknown)			(2.30)	
Clinical						
Griffin[c]	Adult males	11 @ 10.9			(1.40)	
Griffin[c]	Adult males	14 @ 3.2			(1.65)	
Rabinowitz[c]	Adult males	2			(1.7, 2.5)	
Gross[d]	Adults	(21,000 person-days)			(0.38)	
Chamberlain[d]	Adults	7			(1.20)	
Chamberlain[d]-Kehoe	Adults	5			(1.10)	

[a] U.S. EPA, 1977.

[b] Authors regression equation evaluated at specific air lead.

[c] U.S. EPA calculation

[d] Authors calculations

[e] Ratios presented in parentheses are not calculated from any regression equation.

Dose-effect relationships such as may be derived from the Azar data are conceptually useful, but are not as satisfactory as dose-response analyses wherein one can estimate the proportion of people who would exceed any specific PbB at any specific air lead level. Only the Azar data could be used for this purpose. Dose-response relationships as calculated from the Azar data by the U.S. EPA (1977) are presented in Table 3.

TABLE 3

Estimated Percentage of Population Exceeding a Specific Blood Lead Level in Relation to Ambient Air Lead Exposure[a]

Air lead, μg/m^3	Percent exceeding blood lead level of: 20.0 μg/dl	30.0 μg/dl	40.0 μg/dl
0.5	15.22	0.59	0.02
1.0	26.20	1.67	0.07
1.5	34.12	2.88	0.16
2.0	40.23	4.12	0.26
2.5	45.15	5.35	0.38
3.0	49.23	6.57	0.51
3.5	52.69	7.75	0.66
4.0	55.67	8.90	0.81
4.5	58.27	10.01	0.97
5.0	60.57	11.09	1.14
6.0	64.45	13.16	1.48
7.0	67.63	15.10	1.83
8.0	70.28	16.92	2.20

[a] Azar, et al. 1975.

So far as the contribution of other sources of lead to PbB is concerned, a quantitive analysis such as has been done for air lead is simply not possible using the data currently available. An estimate of the total dietary contribution to PbB was attempted by World Health Organization recently (Table 4).

TABLE 4

Comparison of Daily Oral Lead Intake With PbB Levels[a]

Study Design	Oral Intake (μg/day)	PbB[b] (μg/100 ml)	PbB per 100 μg oral Pb	Reference
Duplicate portion	113 (men)	20.7	18.3	Coulston, et al. (1972)
Fecal excretion	119[c] (women)	15.3	13.0	Tepper & Levin (1972)
Duplicate portion	230 (men)	12.3	5.4	Nordman (1975)
Duplicate portion	180 (women)	7.9	4.4	Nordman (1975)
Composites technique	505 (men)	34.6	6.8	Zurlo & Griffini, 1973[d]

[a] WHO, 1977.

[b] Contributions of air to PbB levels are not reported in most of these studies and could not be subtracted from total PbB levels.

[c] Calculated from daily fecal excretion of 108 μg of lead assuming gastrointestinal absorption 10%.

[d] PbB levels from Secchi, et al. (1971).

The great discrepancy between American and European data cannot be explained. It should be noted, however, that the Coulston subjects were prisoners, whose diet perhaps is far from typical and that the Tepper and Levin data were based on fecal lead excretion, adjusted upward to compensate for an assumed 10 percent lead absorption. The European data are impressive in that they are consistent among studies over a fairly wide range of PbB's and dietary intake levels, with a range of 4.4 to 6.8 and an average of 5.5.

So far as the contribution of water specifically is concerned, information is even scarcer than for total diet. Estimates of the contribution of lead in water to PbB have been reported in four separate studies. The first of these was published in 1976 (Elwood, et al. 1976). A linear regression was calculated for PbB and water lead using "first run" morning tap water in 129 houses in northwest Wales. Blood lead concentrations were determined for an adult female resident in each house. The regression drawn was as follows:

$$\text{PbB } (\mu g/dl) = 19.6 + 7.2 \text{ (mg Pb/l water)}$$

The regression selection seems inappropriate from examination of the scattergram (Figure 1). A curvilinear model would have been more appropriate or at least should have been tested, particularly since the authors' linear model extrapolates to PbB - 19.6 μg/dl, a rather high baseline value for non-occupationally exposed women.

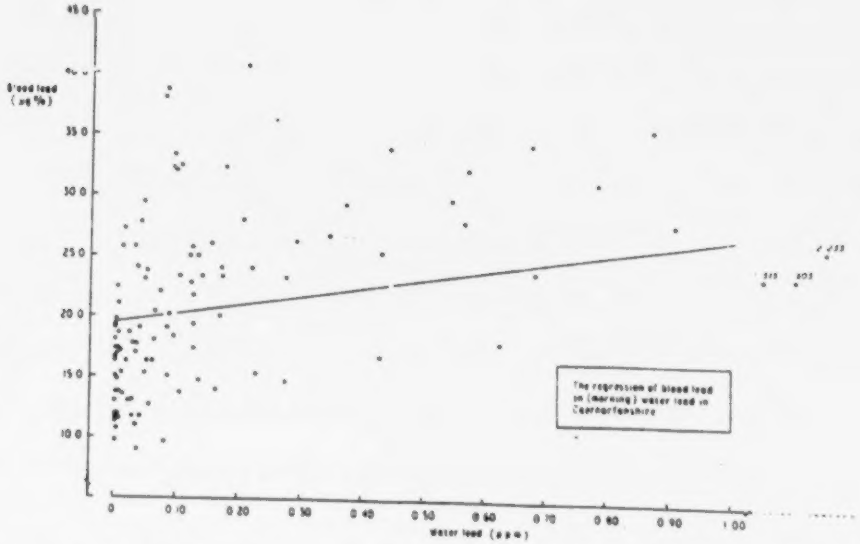

Figure 1. Regression of blood-lead on morning water lead in Caernarfonshire (Elwood, et al. 1976).

Moore, et al. (1977a) reported a very similar study in which the interaction of PbB with lead in both "first flush" water and running water was determined (Moore, et al. 1977a). The study was conducted in Glasgow, Scotland, where the water is extremely soft. As in the Elwood study, blood was drawn from adult females of the household.

The Moore, et al. study demonstrated that there is a curvilinear relationship between PbB and the concentration of lead in "first flush" water (Figure 2).

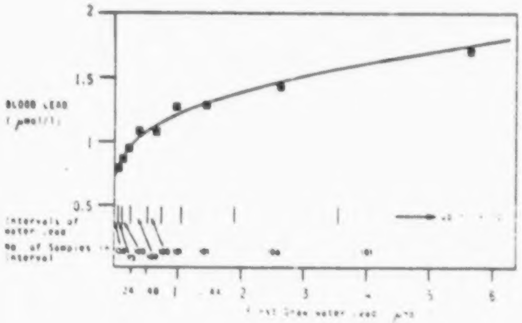

Figure 2. Mean blood-lead values for nine groups at intervals of first-flush water lead (Moore, et al. 1977a).

The equation for the regression line was $x = 0.533 + 0.675 y$, with both values being expressed as µmol/l. Blood lead rose as the cube root of "first flush" water. Actually, there is an error in the equation. The term x really is PbB and y is the cube root of the "first flush" water. The authors point out that the lead concentration in running water probably reflects the impact of drinking water on PbB better than "first flush" water. They found that the same relationship held, wherein mean blood lead rose in proportion to the cube root of running water lead. The correlation of running water lead to PbB was even somewhat better than that of "first flush" water to PbB ($r = 0.57$ vs. $= 0.52$). According to the authors, running water lead concentrations were approximately one-third the "first flush" lead concentrations. These data are useful in that they provide an estimate of the consequences of changing the concentration of lead in water from one value to another. The example provided is the PbB consequence of going from a "first flush" concentration of 0.24 µmol/l (50 ug/l) to 0.48 µmol/l (100 µg/l). Such a change results in an incremental rise in PbB of 0.11 µmol/l, or of 2.3 µg/dl. On a running water basis, the PbB change would occur going from 24/3 or 8 µg/l to 48/3 or 16 µg/l. Using the authors' equation, the effect of lead in running water on PbB can be estimated (Table 5).

TABLE 5

Effect of Running Water Lead on PbB Based on Results of the Moore, et al. (1977a) Study

Pb in levels (µmol/l) (y^3)	(y^3) Pb levels in running water[a] (µg/l)	Total PbB	PbB due to water
0	0	11.03	0
0.0145	1	14.44	3.41
0.0725	5	16.86	5.83
0.1449	10	18.37	7.34
0.3623	25	20.99	9.96
0.7246	50	23.58	12.55
1.4493	100	26.84	15.81

[a] $y = \frac{(\mu g \text{ of Pb/l of running water})}{207} \times 3$

If this relationship is correct, the impact of water lead on PbB is extremely great in the lower ranges of water lead but diminishes rapidly in the higher range of water lead = 50 to 100 µg/l.

Hubermont, et al. (1978) also reports the interaction of morning tap water lead to PbB in pregnant women of the household. Again, as in the study of Moore, et al. a curvilinear relationship is described for the interaction of PbB with water lead:

$$\text{PbB} = 9.62 + 1.74 \log \text{morning water Pb}, (\mu g/l)$$

The correlation was good ($r = + 0.37$; p 0.001). The calculated impact of water Pb on PbB using this equation is considerably less in the lower range of water lead than in the Moore, et al. study. The data may not be strictly comparable concerning water sampling procedure.

One additional set of data is available which bears on the question of the impact of the concentration of lead in water on PbB. A study was conducted by the U.S. EPA concerning the relationship of lead in drinking water to PbB (Greathouse and Craun, 1976). Both early morning and running water samples were analyzed for lead in a soft water area (Boston, Massachusetts). In addition, blood samples for members of the household were analyzed for lead. These subjects included both children and adults. Numerous variables that might have influenced PbB were measured, including age, sex, traffic density, lead in dust, and socio-economic status. The data for interaction of PbB and water Pb were reevaluated by Dr. Greathouse specifically for the purpose of comparison to the analyses of Moore, et al. (1977a) and Hubermont, et al. (1978). This was done subsequent to publication of the 1976 Greathouse and Craun report. Statistical analyses were performed using both the Hubermont model (PbB = a + b log Pb in water) and the Moore model (PbB = a + b $\sqrt[3]{\text{Pb water}}$). These models were tested using (1) all subjects aged 20 or more, and (2) women 20 to 50. The models were also tested using running water data and early morning water data. Interestingly, the relationship of early morning water Pb to running water Pb was almost identical to the 3:1 relationship reported by Moore, et al. (1977a). More precisely, the relationship was:

$$\text{early morning water Pb} = -0.028 + 3.081 \text{ running water Pb}$$

$$r^2 = 0.235; \quad p = 0.0001$$

The cube root model of Moore, et al. (1977a) was more appropriate than the log water Pb model of Hubermont, et al. (1978), and the correlation of PbB with running water Pb was better than with morning water Pb. The correspondence between data from all subjects 20 years of age and over and for women age 20 to 50 was striking:

females 20 to 50, $n = 249$

$$\text{PbB} = 13.38 + 24.87 \sqrt[3]{\text{running water, Pb, } \mu\text{g/l}}$$

$$p = 0.020$$

all subjects 20 yrs +, $n = 390$

$$\text{PbB} = 14.33 + 25.41 \sqrt[3]{\text{running water, Pb, } \mu\text{g/l}}$$

$$p = 0.0065$$

At this point it is useful to compare the data from the three studies discussed above. These data constitute the sole firm foundation for assessing the impact of lead in water on the internal dose of lead as reflected in PbB. The comparison is presented in Table 6. Calculations are made as to the PbB due to water over a range of 1 to 100 µg Pb/l. The comparison is made on the basis of running water Pb in spite of the fact that the equations for the two European studies were developed on the basis of "first flush" or "early morning" water. This adjustment seems justified since the ratio of these values to running water values has been affirmed to be 3:1 in two of the three studies and therefore probably is approximately correct for the third study, the one by Hubermont, et al. (1978). It is seen that the impact of lead in water on PbB is quite different among the three studies. Since there is no basis for rejecting any of the three studies, it can only be surmised that an average of the three sets of data is as good an estimate of the average situation as any. The reasons for the variation in the relationships can only be left to speculation.

TABLE 6

PbB Levels due to Water Lead as Predicted by the Moore, et al. (1977a) and the Hubermont, et al. (1978) Studies

Running Water (µg/l)	PbB due to water U.S. EPA, 1978[a]	Moore, et al.[b] (1977a)	Hubermont, et al.[b] (1978)	Average, all 3 studies
1	2.54	3.41	0.83	2.26
5	4.35	5.82	2.05	4.07
10	5.47	7.34	2.57	5.13
25	7.43	9.96	3.26	6.88
50	9.36	12.55	3.79	8.57
100	11.79	15.81	4.31	10.64

[a] Calculated from the data of Greathouse and Craun, (1976).

[b] These values were all calculated using morning or "first flush" water values which were taken to be three times the running water levels in the table.

Certainly the calcium, phosphate, and iron concentrations of the waters in the three studies were different and may, to some extent at least, account for the differences in the impact of lead in water on PbB.

It is known that calcium profoundly depresses lead absorption, even over a relatively narrow range. For example, Ziegler, et al. (1978) demonstrated that a mere doubling of the dietary calcium level profoundly depressed lead absorption in infants. Also, animal studies have shown that nutritional iron deficiency enhances lead absorption. Attention should be given to the significance of the variations in calcium and iron content of water against the background variations of calcium and iron content in non-water elements of the diet. As with calcium, high phosphate levels also tend to depress lead absorption.

EFFECTS

The effects of lead on man will be reviewed in a selective fashion. Greatest emphasis will be placed on those effects which occur at the lower levels of exposure and those which are properly viewed with the most concern, namely neurobehavioral effects, carcinogenesis, mutagenesis, and teratogenesis. Because of the paucity of data in man and the seriousness of the effect, some sections will be specifically subdivided into subsections dealing with human data and animal data. In other cases that does not seem necessary because of the wealth of human data available.

Hematological Effects

There is a vast literature concerning the effects of lead on the formation of hemoglobin and more limited literature on the related effects on other hemo-proteins. From the standpoint of standard setting, the effects of lead on this system are particularly important since current knowledge suggests that the hematopoietic system is the "critical organ." That is to say that effects are detectable at lower levels of lead exposure than is the case with any other organ or system. The mechanism whereby lead reduces the circulating concentration of hemoglobin is not thoroughly understood. Many specific abnormalities exist, some occurring at lower PbB's than others. The lifespan of erythrocytes is shortened in heavy lead exposure (PbB = 59 to 162) (Hernberg, et al. 1967). The mechanism is not well understood, but damage to the erythrocyte membrane is likely. Dose-response and dose-effect relationships have not been established. It seems unlikely, however, that shortened cell life is the most sensitive locus of lead-induced reduction in circulating hemoglobin. Rather, it is more likely that the synthesis of hemoglobin is the critical mechanism.

Although there is evidence that lead interferes with globin synthesis as well as heme synthesis, this effect seems to occur only secondarily to a deficit in heme production (Piddington and White, 1974). Thus, it is the action of lead on heme synthesis that appears most critical. This action is complex and involves several enzymes in the synthesis of heme (Fig. 3).

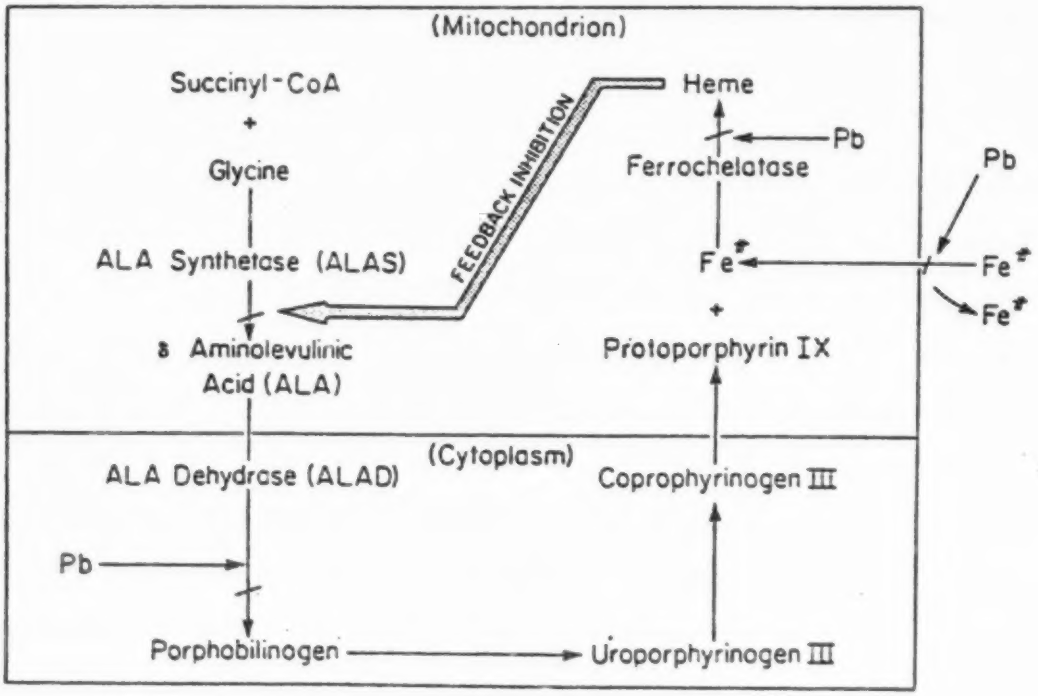

Figure 3. Effects of Lead on Heme Metabolism

Clear evidence exists that lead inhibits both d-aminolevulinic acid dehydrase (ALAD) and heme synthetase both in vitro and in vivo at relatively low levels of lead exposure. Elevation of the concentration of the substrates for these two enzymes in plasma and urine (ALA) and in erythrocytes (PROTO) increases as PbB increases. As a matter of fact, rises in PROTO and ALA occur at PbB's somewhat below those associated with a decrement of hemoglobin. Thus, in adults, a decrement in hemo-globin first appears at PbB = 50 (Tola, et al. 1973) and at PbB = 40 in children (Betts, et al. 1973; Pueschel, et al. 1973), whereas a distinct elevation in ALA in the urine (ALAU) first appears at PbB = 40 in men (Selander and Cramer, 1970; Haeger-Aronsen, et al. 1974) and children (Natl. Acad. Sci/Natl. Res. Counc., 1972) and somewhat lower in women (Roels, et al. 1975). Rises in PROTO first appear at PbB = 15 to 30 in women and children and at PbB = 25 in men (Sassa, et al. 1973; Roels, et al. 1975). The most reasonable explanation for the rise in PROTO at levels of lead exposure below the threshold for hemoglobin decrement is that the primary event is inhibition of the insertion of iron into PROTO IX, whether it is caused by inhibition of heme synthetase or by inhibited entry of Fe into the mitochrondrion (Jandl, et al. 1959). Regardless of that uncertainty, the effect is the same, a potential decrement in hemoglobin which leads to feedback depression of ALAS resulting in a compensatory increase in the production of ALA and other heme precursors. The evidence for this conpensatory adjustment is to be found both in laboratory animal studies (Strand, et al. 1973; Suketa and Yamamoto, 1975) and in studies of people with elevated lead exposure (Berk, et al. 1970; Meredith, et al. 1977). The approximate threshold for ALAD inhibition is PbB = 10 to 20 for adults (Tola, 1973) and PbB = 15 in children (Granick, et al. 1973). Inhibition of roughly equivalent degree occurs concurrently in the liver of man (Secchi, et al. 1974) and in the liver and brain of rats (Millar, et al. 1970). The toxicological implications of ALAD inhibition have not been studied extensively. However, substantial lead-induced depression of blood ALAD activity in dogs does not reduce the blood-regenerating response to acute hemorrhage in dogs (Maxfield, et. al. 1972).

A few studies have been reported concerning effects of lead on hemoprotiens other than hemoglobin. Thus, the rate of cytochrome P450-mediated drug metabolism has been found to be depressed in 2 cases of lead poisoning (PbB = 60 & 72) but not in 10 cases where lead exposure ranged from PbB = 20 to 60 (Alvares, et al. 1975). Cytochrome content of kidney mitochondria has also been reported to be depressed in rats (Rhyne and Goyer, 1971).

The question arises as to whether certain populations may be predisposed to the toxic effects of lead as a result of G-6-PD deficiency or iron deficiency. G-6-PD deficiency is known to be associated with increased susceptibility of erythrocytes to hemolysis. The possibility of increased susceptibility of G-6-PD-deficient children to the hematopoietic toxicity of lead has not been reported. In regard to possible enhancement of hemoglobin deficiency by coexistent iron deficiency, the one study reported to date was negative. There was no significant difference in the blood hemoglobin or hematocrit among 29 iron-deficient children with PbB 20 μg/dl as compared to 17 iron-deficient children with PbB = 20 to 40 μg/dl (Angle, et al. 1975).

Dose-response relationships for the effect of lead on various parameters of hematological indices have been developed recently (Zielhuis, 1975). These are reproduced in tabular form in Table 7.

TABLE 7
Dose Response Relationships for the Effect of Lead on Various Parameters of Hemotological Indices[a]

Percentage of adult female subjects with FEP levels that exceeded those found in control subjects with PbB =20 μg/100ml

PbB level (μg/100 ml)	No.	% with FEP level higher than normal
11-20	28	4
21-30	9	33
31-40	8	90
41-50		
51-60	4	100
61-70		
	49	

Percentage of children with FEP levels that exceeded those found in control subjects with PbB=20 μg/100 ml

PbB level (μg/100 ml)	No.	% with FEP level higher than normal
20	87	5
21-30	72	21
31-40	24	29
41-50	14	
51-60	12	64
61-70	10	
	219	

Percentage of adult male subjects with FEP levels that exceeded those with PbB =20 μg/100 ml

PbB level (μg/100 ml)	No.	% with FEP level higher than normal
11-20	26	0
21-30	43	7
31-40	32	19
41-50	4	
51-60	2	100
61-70	2	
	109	

Percentage of male adults with ALA-U levels = 5 mg/litre and = 10 mg/litre according to PbB level

PbB level (μg/100 ml)	No.	ALA-U level (mg/litre) =5	ALA-U level (mg/litre) =10
11-20	17	0	0
21-30	27	0	0
31-40	36	14	3
41-50	55	33	11
51-60	38	74	37
61-70	34	88	50
	207		

[a] Zielhuis, (1975).

In considering these data, it is obvious that FEP (essentially PROTO) elevation is a more sensitive correlate of lead exposure than ALAU. It should also be noted, however, that an increase in FEP above normal also occurs in iron deficiency anemia. Thus, the data must be considered in that light. In a recent study of FEP in lead-exposed and non-lead-exposed children, Roels, et al. (1978) were able to study the interaction of FEP and PbB in the absence of anemia as indicated by serum iron concentration. They proposed a maximum acceptable limit for FEP at PbB = 25 µg/dl. The maximum acceptable point was the mean FEP plus two standard deviations for rural children, which equalled 79.2 µg FEP/dl erythroytes. The PbB of these children was 9.1 µg/dl + 0.5 with serum iron 50 µg/100 ml. This maximum is very similar to the maximum acceptable FEP which would be calculated from the data of Piomelli at mean FEP plus two standard deviations (PbB = 26 µg/dl) cited in the recent "Air Quality for Lead" (U.S. EPA, 1977a). As was indicated earlier, the cooperative effect of iron deficiency and lead exposure on FEP has not as yet been adequately defined. There is just the one study by Angle, et al. 1975, suggesting no interaction at PbB = 20 to 40.

Neurological and Behavioral Effects

The syndrome of lead encephalopathy has been recognized since the time of Hippocrates as occurring in workers in the lead trades. The major features were dullness, irritability, ataxia, headaches, loss of memory and restlessness.

These signs often progressed to delirium, mania, coma, convulsions, and death. The same general effects were also described in infants and young children. Encephalopathy due to lead was probably more frequently fatal in children than in adults because lead exposure was usually not suspected and because children do not communicate signs and symptoms as readily as adults. The mortality rate among children has been variously reported as being from 5 to 40 percent.

The literature concerning the neurological features and the probable dose of lead involved is far more specific for children than for adults. This is probably because the problem persisted longer and hence benefited more from the accumulated sophistication of disease investigation. Apart from the mortality statistics, there was a considerable toll recorded among survivors in the form of long-term neurological sequelae. Cortical atrophy, convulsive seizures, and mental retardation were commonly reported (Perlstein and Attala, 1966; Byers and Lord, 1943).

The minimal level of lead exposure resulting in lead encephalopathy is not clearly known and perhaps never will be in light of the dramatic decrease in the incidence of the disease, particularly during the last 10 to 15 years. Drawing mainly from his own experiences, Chisolm has estimated the minimal PbB associated with encephalopathy as being 80 ug/dl (NAS/NRC, 1972b). There are occasional reports however of occurrence of encephalopathy at PbB's below 80 µg/dl (Smith, et al. 1938; Gant, 1938). Although 80 µg/dl may be a reasonable estimate of threshold for encephalopathy in children, the usual values are much higher, with a mean of approximately 328 according to one source (NAS/NRC, 1972).

It has been reasoned that if lead exposure as specified above can have such severe deleterious effects on the central nervous system, lower levels of exposure might well result in more subtle effects. Specifically, the concern has been over whether such effects occur in children whose PbB's are in the 40 to 80 µg/dl range. Given the difficulties of study design, it is hardly surprising that all of the relevant studies are open to criticism. The most common deficiencies encountered are overlap of lead exposure in the study groups (Pb versus control), inadequate matching for socio-economic status and other variable, insensitivity of the behavioral tests, and poor knowledge of the degree of lead exposure. In regard to this last-named problem, the index of exposure has usually been PbB's determined at the time of behavioral testing. In some instances record of one earlier PbB determination was available. In spite of these problems, when the various studies are taken together, subtle neurobehavioral effects do appear to occur as a result of exposure in the range of PbB = 40 to 80 ug/dl.

Two general approaches have been used in attacking the problem. The most common approach has been to evaluate two populations of children closely matched as to age, sex, and socio-economic status, but differing as to lead exposure. These studies are retrospective and usually strictly cross-sectional. In only one instance was a follow-up repeat study of the population performed (de la Burde and Choate, 1972; de la Burde and Choate, 1975). The other general approach has been to identify children with neurobehavioral deficits of unknown etiology and to establish whether their lead exposure was excessive in comparison to appropriate control children. Aside from the usual specific flaws in experimental design, there has been the additional question as to which came first, the excessive lead exposure or the neurobehavioral deficit. Among mentally subnormal children whose problems were clearly attributable to etiologies other than lead, pica incidence and PbB's were both elevated (Bicknell, et al. 1968).

Among studies of the first type, those of de la Burde and Choate are illustrative of the problems that exist in this area of toxicology. Fine motor dysfunction, impaired concept formation, and altered behavior profile were observed in 70 preschool children exhibiting pica and elevated PbB's, all of which were < 30 µg/dl. The mean level was 59 µg/dl. The children were examined at 4 years and again at 7 years of age. Both the lead-exposed group and the control group had been followed from infancy through 8 years of age as part of a Collaborative Study of Cerebral Palsy, Mental Retardation, and Neurologic Disorders of Infancy and Childhood. Unfortunately, the control group did not have blood lead analyses performed. However tooth lead and urinary coproporphyrin determinations ultimately were performed. Another problem was that positive radiographic findings of lead in long bones and/or intestines were inferred to have been found in subjects with PbB's in the range of 30 to 40 µg/dl. Lead lines in bones at this level of exposure are extremely unlikely (Betts, et al. 1973), suggesting either that the blood lead determinations were spuriously low or that they had actually been higher at times which did not coincide with the time of sampling. Thus, it would seem that the minimal PbB associated with neurobehavioral effects may well have been more on the order of 50 to 60 µg/dl rather than 30 to 40 µg/dl. Overall, the experimental design was otherwise generally sound.

Another oft-quoted study by Perino and Ernhart (1974) was basically of the same general design as the one reported by de la Burde and Choate. It concluded that neurobehavioral deficits occurred at PbB's as low as 40 µg/dl. The flaw in this study was that the parents in the control group were better educated than those of the lead-exposed children. Differences found may have been due to the fact that more highly educated parents train their children more on tasks related to the behavioral measures used. Low lead parent-child intelligence was correlated at 0.52 and high lead at only 0.1. The low correlation in high lead groups suggests that a factor other than parental influence was operating and probably was lead exposure.

Albert, et al. (1974) studied school-age children who had had PbB's $>$ 60 µg/dl early in childhood. Unfortunately, PbB's for about one half of the control population were not available and some of the control children had had PbB's $<$ 40 µg/dl.

The same types of flaws existed in studies which came up with negative results. Thus, Kotok's study (Kotok, 1972) had a rather wide overlap between PbB's of control subjects and lead-exposed subjects, and in another negative study fewer than half of the "lead-exposed" group had PbB's > 40 µg/dl (Lansdown, et al. 1974). Another problem among negative studies has been the study of perhaps inappropriate populations. Lansdown's population consisted of British children living in the vicinity of a smelter. In another negative study, the children were Mexican-Americans also living in the vicinity of a smelter (McNeil, et al. 1975). The problem population we are dealing with in this country is of an entirely different socio-economic character; inner city children who are predominantly socially and economically deprived. The difference in background may be significant as a determinant of behavioral ability.

In summary, there is sufficient evidence to indicate that subtle neurobehavioral effects of lead exposure occur in children exposed to lead at levels which do not result in clinical encephalopathy. The minimal level of lead exposure, the duration of exposure required, and the period of greatest sensitivity cannot be specified with any degree of certainty. However, the conclusions of two recent expert groups who have evaluated the literature in great depth are remarkably similar. The World Health Organization concluded that the probability of noticeable brain dysfunction increases in children from PbB levels of approximately 50 µg/dl (WHO, 1977), and the U.S. Environmental Protection

Agency's Science Advisory Board concurred in the U.S. EPA conclusion that "the blood lead levels associated with neurobehavioral deficits in asymptomatic children appear to be in excess of 50 to 60 µg/dl". Future research may reveal that this cut-off point is actually lower. Effects of lead exposure on the peripheral nervous system of both adults and children are also documented. A number of studies have documented the occurrence of slowed nerve conduction with an approximate PbB maximum of 50 µg/dl (Hernberg, et al. 1967; Lilis, et al. 1977; Landrigan and Baker, 1976). This effect has been noted to occur at this exposure level without any overt signs of neuromuscular impairment.

Although generally considered not to be a major public health problem today, the potential damage to the brain of the fetus from lead exposure has received some attention. Beattie, et al. (1975) identified 77 retarded children and 77 normal children matched for age, sex, and geography. Of 64 matched pairs, 11 of the retarded children came from homes in which the concentration of lead in the "first flush" water exceeded 800 µg/l. By contrast, none of the control children came from such homes. In a follow-up study, PbB's from the mental retardates, taken during the second week of life, were found to be significantly higher than those of control subjects (25.5 µg/dl versus 20.9 µg/dl) (Moore, et al. 1977b). Taken at face value, those studies are extremely provocative. They suggest that the brain of the fetus is considerably more sensitive to the toxic effects of lead than the brain of the infant or young child. Lambs exposed to low levels of lead in utero (PbB = 35) developed impaired visual discrimination learning behavior (Carson, et al. 1974). In spite of this seemingly low level of exposure, control animals were exposed in utero to lower levels of lead (PbB = 5) than are generally considered normal for most species. Bull and coworkers have exposed female rats to Pb from 14 days prior to breeding through weaning of pups. The normal postnatal increase in cerebral cytochromes (Bull, et al. 1978) and synaptogenesis in the cerebral cortex (McCauley, et al. 1977) were delayed by this treatment. These delays were associated with delays in the development of exploratory and locomotor behavior during the same development period (Crofton, et al. 1978). The latter effect was shown to be entirely due to exposure to Pb in utero. Blood lead concentrations on the 18th day of gestation were reported to be 31.9 μg/dl. Further work is urgently needed concerning the neurobehavioral effects of low-level lead exposure in utero.

Finally, a few comments are in order regarding neurobehavioral effects of low-level exposure in adults. A battery of performance tests were administered to 190 lead-exposed workers, along with a questionnaire concerning affected (Morgan and Repko, 1974). PbB's were below 80 μg/dl in many of the workers. Unfortunately, there were many methodological problems and equipment failures which rendered the results difficult to interpret. Further, results of a similar study by other investigators were essentially negative (Milburn, et al. 1976). Thus, although it seems reasonable to suppose that neurobehavioral effects do occur at some level of exposure in workers, it is extremely difficult to specify the exposure level at which these effects may occur.

Carcinogenicity

Human Studies

Three groups of investigators have reported epidemiological studies of causes of death among people overly exposed to lead. The first such study was of causes of death among 184 pensioners who died between 1926 and 1961 and of 183 men who died between 1946 and 1961 while still employed (Dingwall-Fordyce and Lane, 1963). The men were categorized as to lead exposure based on the nature of their work and, in the case of highly exposed men, on the basis of urinary lead excretion (100 to 250 µg/dl during the past 20 years and probably higher than that earlier in the work history). There is a correlation between urinary lead and blood lead, wherein 100 µg Pb/l in urine corresponds roughly to 50 µg/dl in blood (Selander and Cramer, 1970).

There were 179 men in the high exposure category for which causes of death were registered, 67 men in the category of negligible exposure and 91 men with no exposure. Although there was a significant excess number of deaths among the men who had been exposed to the greatest lead hazard, this excess could not be attributed to malignant neoplasms, as the mortality rate from this cause was actually somewhat less than expected. Furthermore, the incidence of death from malignant neoplasms in this group has actually increased in the more recent years as working conditions have improved. It seems, rather, that the excess deaths in the heavily-exposed group was due mainly to vascular lesions of the central nervous system among men employed in the lead industries during the first quarter of this century.

The second relevant study was of orchardists who at one time sprayed fruit trees with lead arsenate. A cross-sectional study of this population was conducted in 1938 by the U.S. Public Health Service. The population was classified as to exposure on the basis of whether they were adult orchard workers, (orchardists and lesser-exposed "intermediates" as separate categories), non-exposed adults of the area, and children in the area. For all categories blood lead and urine lead and arsenic concentrations were determined. In addition, the number of years of spray exposure was recorded for the orchardists and "intermediates." There was a definite gradation in blood and urine lead concentration corresponding to the degree of exposure as classified by nature of orchard-related work or lack thereof. The orchardists had the highest PbB (x = 44 for males and 43 for females). Children of the area were intermediate (PbB = 37 in boys and 36 in girls) and adult consumers and "intermediates" had PbB's of 22 to 30.

In 1968 a follow-up study of this population was begun. Results were reported in 1973 (Nelson, et al. 1973). Of the original 1229 study members, the status of 1175 could be determined. Four hundred and fifty-two had died and death certificates were available for 442. No consistent differences in Standard Mortality Ratios (SMR) were observed on the basis of either exposure classification or duration of exposure. The only deviations in SMR from expected were in the direction of fewer-than-expected deaths. The mortality record for heart disease, cancer, and stroke were examined separately. Again, there was no suggestion of a relationship between lead exposure and death from any of these three major causes of death.

The most recent study of causes of death among lead-exposed workers was reported by Cooper and Gaffey (1975). Since the results were published, the study population has been reexamined (Cooper, 1978). Results from the updated study will be discussed, although details as to lead exposure history appear mainly in the 1975 publication. The objective of the study was to determine what happened to lead workers whose levels of lead absorption were below those associated with clinically-recognizable illness but above that of the general population. The population studied consisted of 2,352 smelter workers and 4,580 battery workers. Death certificates were available for 1,703 of these men. A good record of lead exposure history was considered important. Unfortunately biological monitoring programs (lead in urine or blood) were not in effect in many of the plants during the period of employment, particularly so for the deceased. Nevertheless, enough data were available to indicate that exposure was heavy. Thus, 67 percent of 1863 workers had PbB's $\geq$ 40 ug/dl and 20 percent had PbB's 70-$\geq$ ug/dl. Twenty-six percent of the battery workers and 21.1 percent of the smelter workers had been employed for more than 20 years.

The only causes of death that showed a statistically significant elevation were "all malignant neoplasms" in the battery workers, cancers of "other sites" in battery workers and "symptoms, senility, and ill-defined conditions" in battery workers. In only one of all the cancer deaths was a renal tumor specified. Only two tumors of the brain were identified in the follow-up study. (No specification is made in the original 1975 report as to brain tumors.)

The author of the 1978 report concludes that the excess deaths due to neoplasms cannot be attributed to lead "because there was no consistent association between the incidence of cancer deaths and either length of employment or estimated exposures to lead." It is not clear from reading either of the two reports concerning this population as to just how exposure categories were established.

Animal Studies

In 1953 a study was published indicating that lead causes renal tumors in rats (Zollinger, 1953). Since that time five other studies have confirmed this finding (Boyland, et al. 1962; Van Esch, et al. 1962; Roe, et al. 1965; Mao and Molnar, 1967; Oyasu, et al. 1970). The same observation has also been reported in mice but could not be elicited in hamsters (Van Esch and Kroes, 1969). Other studies indicate that lead also causes lung tumors in hamsters (Kobayshi and Okamoto, 1974) and cerebral gliomas in rats (Oyasu, et al. 1970).

All of these studies were conducted using levels of lead exposure far in excess of tolerable human doses. In its assessment of the available literature the International Agency for Research on Cancer (IARC, 1972) commented as follows:

> It must be noted that the level of human exposure equivalent to the levels of lead acetate producing renal tumours in rats is 810 mg per day (550 mg Pb). This level appears to exceed by far the maximum tolerated dose for man.

As will become apparent in the discussion of the seven substantive papers dealing with experimentally induced cancer, signs of lead poisoning and even high mortalities often supervened using the cancer-inducing dosage regimens. It will also become apparent that none of the studies were designed in anticipation of subsequent use of the data for the purpose of extrapolating to low incidence doses. Few of the studies utilized more than one dosage level and only one utilized more than two dosage levels. An additional problem is the non-comparability of the modes of administration from one study to another. This makes it impossible to pool data or to compare dose-response curves for consistency.

The first report of lead-induced renal tumors (Zollinger, 1953) was essentially a lifetime study in rats, with administration of lead beginning at 150 to 180 grams body weight and continuing for up to 9.5 months. Single weekly doses of 20 mg lead phosphate were administered subcutaneously. Of the 112 animals on lead that were examined, many died early in the study. Twenty-one had tumors. Of the 29 animals remaining after 10 months, 19 had tumors. The last animals were killed 16.5 months after initiation of the lead injections. All the tumors were renal and were classified as adenomas, cystadenomas, or papillary adenomas. Metastases were evident in only one case, according to the text. All the animals receiving lead had severe lead intoxication, according to the author's histological criteria as applied to the kidneys. Among 50 control animals, none developed tumors.

The next study reported (Boyland, et al. 1962) tested the hypothesis that renal cancer due to lead was actually caused by the well-known accumulation of porphyrins associated with lead toxicity. To test the hypothesis, elevated prophyrin excretion was stimulated by administration of allyl-isopropylacetamide (AIA) in the diet of 20 rats for one year. A like number of rats were fed 1 percent lead acetate in their diet for one year. Both groups of animals were observed until they became ill or had palpable tumors. During the period of lead administration the mortality rate in the two groups was quite similar. Subsequently the lead-fed rats died earlier than the AIA rats. Subsequently to the 1-year administration of test compounds all but one of the lead-fed rats had renal tumors whereas none of the AIA group had tumors of any kind. It is not clear whether the accelerated mortality among the lead-fed rats was due to the tumors or to other toxic effects of lead.

Van Esch, et al. (1962) presented the first study in which tumor mortality was determined at more than one dosage level of lead. In this case lead was administered in the diet as basic lead acetate, 0.1 percent in one group and 1.0 percent in the other. Approximately equal numbers of males and females were used. Each lead-fed group was compared to its own set of controls, not receiving lead. Prior to the termination of the experiment, only moribund animals were killed and examined morphologically. At equivalent durations of lead administration, using these guidelines for tumor assessment, the higher dose of lead was more carcinogenic than the lower dose. Thus, at the end of 600 days of lead administration, 31 percent of the animals which survived to 400 days died with renal tumors in the 1.0 percent lead acetate group, whereas only 14 percent of the animals alive at 400 days in the 0.1 percent lead acetate group died with renal tumors (see Figure 4). Mortalities with tumors in the subsequent 200-day period (600 to 800)

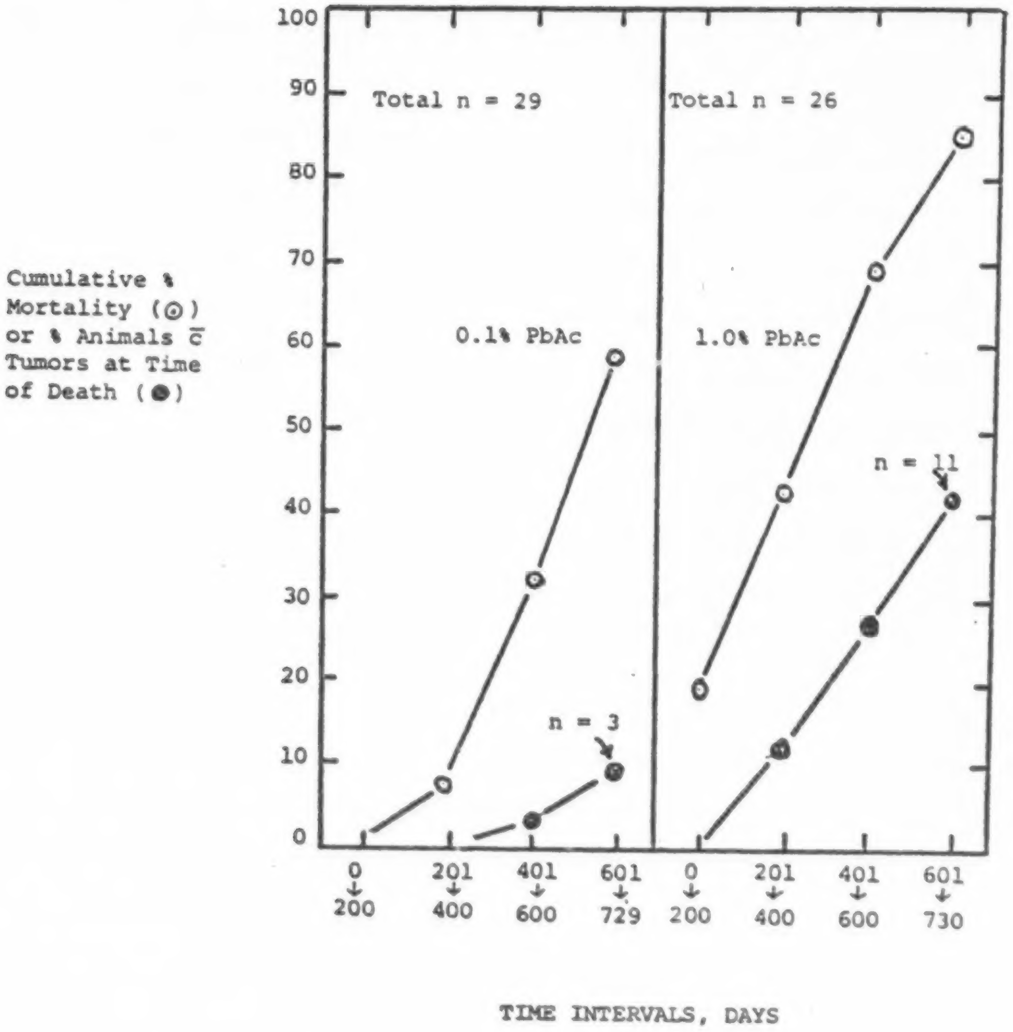

Figure 4. Cumulative mortality and tumor incidence in rats (Van Esch, et al. 1962).

were not comparable because in the case of the 1.0 percent lead group all the animals were killed at 730 days, whereas in the case of the 0.1 percent lead group the animals were allowed to survive until 985 days unless they became moribund. It should also be noted (see Table 8) that during the first 600 days of the 0.1 percent basic lead acetate regimen, 10 of the original 26 rats (38 percent) died without renal tumors as compared to 1 of the original 26 in the control group (4 percent), indicating that at this level the lead regimen was of itself lethal in some manner unrelated to its carcinogenicity. As a matter of fact, both levels of lead administration caused reduced body weight gains, suggesting toxicity unrelated to carcinogenesis.

The next study of lead-induced tumors in rats was also designed to shed light on the mechanism of lead carcinogenesis rather than to define dose-response relationships. Roe, et al. (1965) sought to establish whether testosterone or xanthopterin would influence the induction of renal neoplasms by lead in rats. In this study, the form of lead, lead orthophosphate, and the mode of administration were unique. The lead salt was administered subcutaneously once weekly for 4 weeks, then intraperitoneally for 9 weeks; then after a rest period of 9 or 4 weeks, depending on the particular group of rats, lead administration was resumed for an additional 14 weeks. All the animals were males. The dosage schedule of lead is presented below, assuming an average body weight of 400 g, and averaging the dose over the total treatment period (Table 9).

TABLE 8

Effect of Lead Exposure on the Incidence of Renal Tumors in Rats[a]

	Successive Time Intervals, Days											
	0-200		201-400		401-600		601-729		601-800		800-985	
	C[b]	0.1[c]	C	0.1	C	0.1	C	0.1	C	0.1	C	0.1
n @ beginning of interval	15	16	13	16	12	15	10	14	10	14	5	6
dead, no renal tumors	2	0	1	1	2	1	3	1	5	6	5	1
dead, renal tumors	0	0	0	0	0	0	0	3	0	2	0	5
n @ beginning of interval	14	16	14	16	12	15	9	9	9	9	3	5
dead, no renal tumors	0	0	2	1	3	6	4	4	6	3	3	1
dead, renal tumors	0	0	0	0	0	1	0	0	0	0	0	4
	C	1.0[d]	C	1.0	C	1.0	C	1.0	C	1.0		
n @ beginning of interval	13	11	13	10	12	7	13	5	13	5		
dead, no renal tumors	0	1	0	1	1	1	0	1	12	1		
dead, renal tumors	0	0	0	2	0	1	0	2	0	4		
n @ beginning of interval	13	13	13	9	13	6	13	2	13	2		
dead, no renal tumors	0	4	0	2	0	1	0	0	13	0		
dead, renal tumors	0	0	0	1	0	3	0	2	0	2		

[a] Van Esch, et al. 1962.
[b] C = Control
[c] 0.1 = 0.1% basic lead acetate in diet
[d] 1.0 = 1% basic lead acetate in diet

TABLE 9

Dosage Schedule used by Roe, et al. (1965) in their Study of the Influence of Testosterone and Xanthopterin on the Induction of Renal Neoplasms by Lead in Rats

Group	Pb, mg/kg/d	Days on Pb	n
Pb alone	2.63	242	24
Pb alone	1.25	238	24
Pb alone	0.17	238	24
Pb + testosterone	1.25	238	16
Pb + xanthopterin	1.25	238	16
Pb + testosterone	0.17	238	16
Pb + xanthopterin	0.17	238	16
Xanthopterin	-	238	16
Testosterone	-	238	24
No treatment	-	238	24

In analyzing the cancer data for these groups, it seems reasonable to pool all the groups receiving the same dosage of lead since neither testosterone nor xanthopterin influenced the tumor incidence. However, xanthopterin alone seemed to increase the mortality rate whereas testosterone alone did not. Therefore, only the lead alone, the lead plus testosterone, and the no treatment and testosterone alone groups are pooled here at equivalent lead dosages. The results are summarized in Table 10.

It is not possible to establish the slope of the interaction between dosage of lead and tumor incidence. The highest dose was so toxic that there were only two survivors by the time the first tumor appeared in that group (Table 10). The remaining two dosage levels, by contrast, did not cause death unrelated to tumorigenesis (Fig. 5). However, since only one of these two remaining dosage levels was tumorigenic, no dose-response relationship in regard to tumorigenesis is calculable.

TABLE 10

Summary of Mortality Data Resulting from Lead Phosphate Administration to Rats[a]

Successive Time Intervals, Days

	0 - 100				101 - 200				201 - 300				301 - 400				401 - 500				501 - 600				601 - 700			
	C[b]	2.6[c]	1.3[c]	.17[c]	c	2.6	1.3	.17	c	2.6	1.3	.17	c	2.6	1.3	.17	c	2.6	1.3	.17	c	2.6	1.3	.17	c	2.6	1.3	.17
n at beginning of interval	48	24	40	40	48	6	37	40	48	3	37	38	46	2	37	34	41	1	35	25	26	-	14	18	11	-	6	
dead, no renal tumors	0	18	3	0	0	3	0	2	2	1	0	4	2	0	1	9	15	0	7	7	15	-	5	16	11	0	1	
dead, renal tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	14	0	1	-	3	0	0		5	
in interval dying with tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	50	3	0	2	100	40	0	4	-	57	0	0	-	83	
cumulative mortality, no tumors	0	32	18	0	0	95	18	5	4	100	18	15	9	100	24	37.5	41	100	65	55	74	100	94	95	100	100	100	100
cumulative mortality, tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	4	3	0	2	4	35	0	4	-	45	0	4	-	58	

[a] Roe, et al. 1965

[b] C = controls

[c] average dose of lead phosphate, mg/kg/day

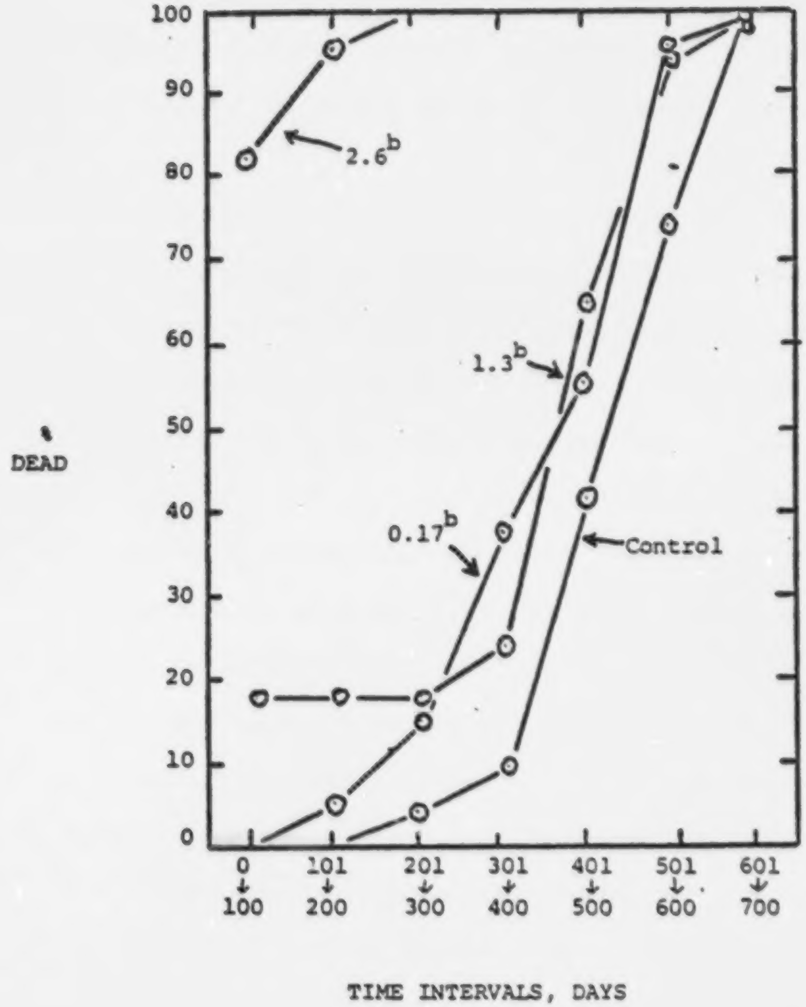

Figure 5. Cumulative mortality among rats not having renal tumors (Roe, et al. 1965).

Interstitial nephritis occurred in all groups, including controls. Unfortunately, other manifestations of toxicity, e.g., anemia, reduced body weight gains, and food consumption were not reported. In keeping with the observations of Van Esch, et al.; Boyland, et al.; Mao and Molnar; and Zollinger, very few of the affected animals exhibited metastasis and no elevated incidence of other types of tumors was noted.

Neither of the two remaining reports concerning the carcinogenic effects of lead in rats (Mao and Molnar, 1967; Oyasu, et al. 1970) involved more than one level of lead administration. The results obtained by Mao and Molnar serve to confirm the results of Van Esch, et al. in that both groups used the same regimen of lead in the diet (1 percent lead acetate) and got similar incidences of renal tumors (50 percent by Van Esch vs. 77.5 percent by Mao and Molnar). Both also noted that the first appearance of tumors was at about 300 days following initiation of lead administration. Mao and Molnar are the only authors who conducted any lead analyses. They reported 19.3 to 54.2 µgPb/g kidney cortex as compared to 3.1 µgPb/g in a single normal specimen. By way of comparison to man, Barry (1975) reported a mean of 0.66 µg/g in kidney cortex of 10 occupationally-exposed adult males, with a standard deviation of ± 0.56 µg/g.

Oyasu, et al. (1970) used a dietary regimen of lead subacetate for 326 to 432 days, either alone or combined with indole in one case and acetylaimofluorene (AAF) in the other. Neither of these substances alone caused renal tumors. Therefore, the data for lead with and without these additional substances could be combined. Fifty-nine percent of 130 animals receiving 1 percent lead sub-acetate in the diet eventually developed renal tumors. This report, incidentally, is the only one in which oral feeding of lead was to cause tumors other than renal. Eight percent of the 130 lead-fed rats developed gliomas. All but one of these were cerebral. One was cerebellar. The incidence of gliomas in animals receiving AAF alone was 2.5 percent, compared to 0.3 percent in controls. There did not seem to be any synergistic effect between AAF and lead. Lead did not cause any other types of tumors. The toxic effects of lead in this study, apart from carcinogenesis, were not reported.

Van Esch and Kroes (1969) have reported that basic lead acetate causes renal tumors in mice, but not in hamsters. These were lifetime studies with lead being incorporated into the diet beginning at 5 weeks of age for the mice and 3 to 4 weeks of age for the hamsters. Two levels of lead were used, 0.1 percent and 1 percent, cut back to 0.5 percent early in the study owing to toxicity. Only one renal tumor was found at the high level of lead intake in the mice, but this was probably because most of the mice died within the first 100 days of lead administration. Fourteen percent of the mice receiving 0.1 percent basic lead acetate developed renal tumors. There were no renal tumors in hamsters at either dosage level of lead. Mortality was somewhat increased at both levels of lead administration.

Another report of experimental carcinogenesis is a report of induction of lung tumors in Syrian hamsters using intratracheal injection of lead oxide (Kobayachi and Okamoto, 1974). Actually, tumors were produced only when benzo (a) pyrene (BP) was injected simultaneously with lead oxide. Neither compound alone caused tumor formation under the conditions described. This cooperative effect was obtained using 10 weekly injections. The tumors were predominantly adenomas of bronchio-alveolar origin. In addition to this effect, both lead alone and in combination with BP caused a very high incidence of alveolar metaplasia, which the authors speculate may be a preneoplastic change. BP alone caused a very low incidence of alveolar metaplasia. All treatments, including the methylcellulose injection vehicle alone caused some deaths. The amount of lead per dose was 1 mg as the oxide, or 0.92 mg as Pb. Assuming a body weight of 100 g, this represents 92 mg/kg over 70 days or 1.3 mg/kg/day. By way of perspective, an adult human breathing lead constantly at 6 $\mu g/m^3$, which is a typical freeway air concentration would receive by tracheo-bronchial and alveolar deposition 6 $\mu g/m^3$ x 20 m^3 x 0.3 or 36 $\mu g/d$ or 36/70 or 0.5 $\mu g/kg$ body weight per day. The hamsters were receiving 2600 times this amount in their lungs on an equivalent body weight basis.

The final study concerning the carcinogenic effects of lead is the most significant of all (Azar, et al. 1973). It confirms other studies showing that lead causes renal tumors in rats and that male animals are more susceptible than females. A dose-related effect is clearly evident (Table 11 and Figure 6).

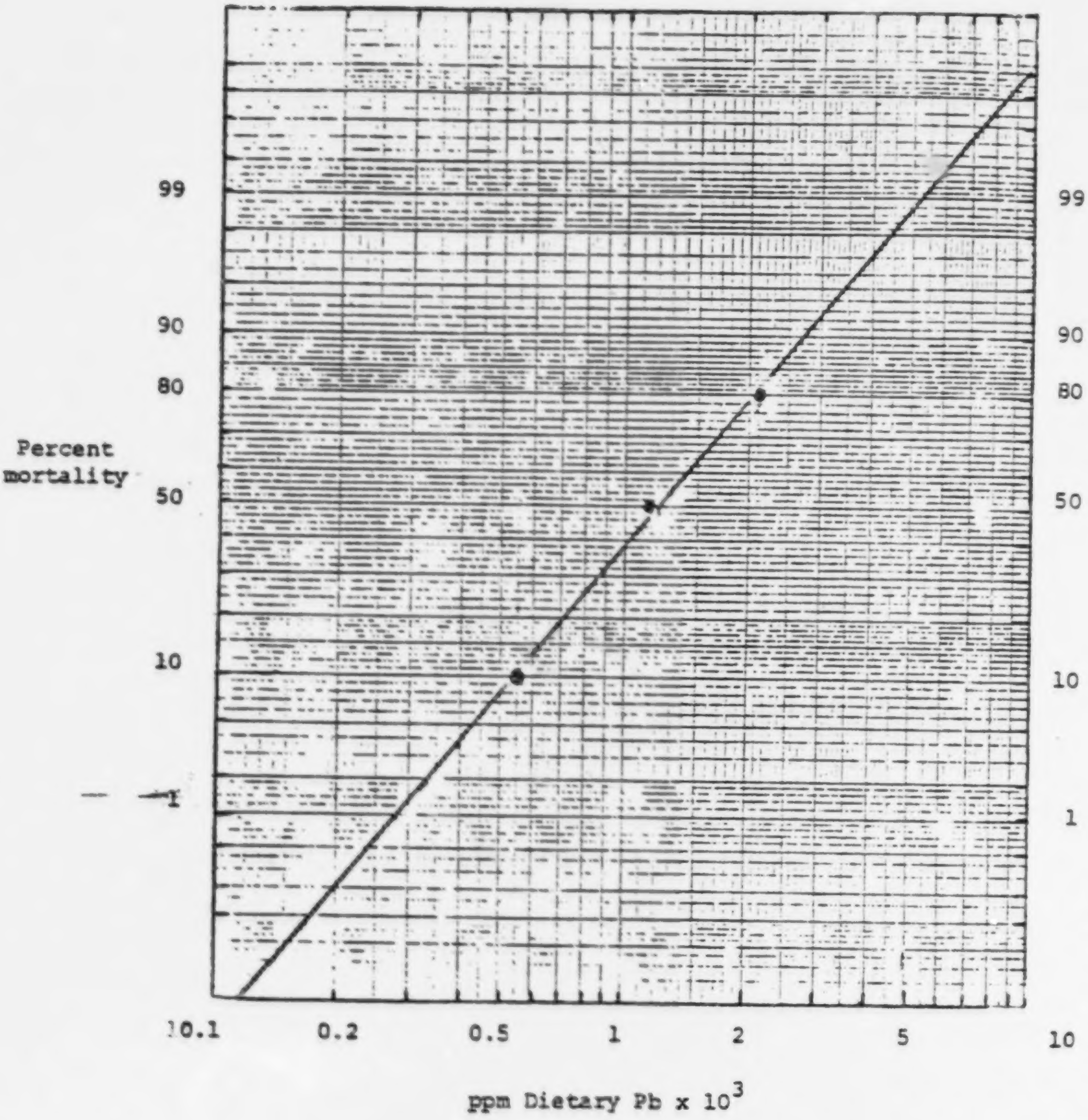

Figure 6. Probit Plot of Incidence of Renal Tumors in Male Rats (Azar, et al. 1973).

TABLE 11

Mortality and Kidney Tumors in Rats Fed Lead Acetate for Two Years

Dietary Pb[a] (ppm)	No. of rats of each sex	% Mortality[b] Male	% Mortality[b] Female	% Kidney tumors Male	% Kidney tumors Female
5	100	37	34	0	0
18	50	36	30	0	0
62	50	36	28	0	0
141	50	36	28	0	0
548	50	52	36	10	0
3	20	50	35	0	0
1130	20	50	50	50	0
2102	20	80	35	80	35

[a] Measured concentration of Pb in diet.
[b] Includes rats that died or were sacrificed in extremis.

The dose of lead required to produce tumors did not clearly result in increased mortality among the animals; however, at dietary lead intake above 1000 ppm, weight gains were reduced. Since a clear dose-response relationship was evident, it was possible to use the data to calculate a risk assessment for cancer in man, utilizing the procedure suggested by the EPA Cancer Assessment Group (see Methodology Document). The safe dose for man was estimated to be 29 ug Pb/l of water.

Summary and Evaluation of Animal Data

There is little doubt that lead is a carcinogen or at least a co-carcinogen in some species of experimental animals. There is some suggestion that bronchial adenomas can be induced in combination with benzo-a-pyrene and that oral administration of lead alone can induce gliomas. These observations need confirmation. Furthermore, in both cases there is no way of constructing a dose-response curve for the effect since only one dosage regimen of lead was used. Even in the case of the numerous studies that have demonstrated the occurrence of renal tumors with lead administration, in only three cases has more than one dosage level of lead been used. Among these three studies, two involved rats and one involved mice. The study by Roe, et. al. 1965, is not amenable to dose-response analysis. Three dosage levels of lead were utilized, initially with a substantial number of animals in each group (Table 9). Unfortunately, 75 percent of the animals at the high dose died of lead toxicity early in the study, before any tumors were formed. This reduced the population to six animals at 100 days and to only two animals at the time the first tumor was observed. Of the two remaining dosage levels, one was a no effect level (no tumors), thereby leaving only one dosage level at which some tumor incidence could be meaningfully assessed. No slope could be estimated.

The second of the three potentially useful studies for dose-response estimates was the one reported by Van Esch, et al. 1962. These data are summarized in Table 8. The data for the two lead-treated groups (0.1 percent and 1.0 percent) are comparable only up to day 730. Beyond that point the groups were handled differently. The 0.1 percent lead group was carried on to day 985 before the survivors were killed, whereas in the case of the 1.0 percent lead group, the survivors were killed at about day 730. If one calculates mortality data up to the time at which the 1.0 percent lead group was killed, a set of cumulative mortality curves can be depicted (Fig. 4). Although a comparison of mortality and tumor incidence is possible at the two doses, the significance is uncertain because of the small numbers of animals involved. The mouse data of Van Esch's group (Van Esch and Kroes, 1969) are not useful for constructing dose-response curves because only one dose level of lead caused tumors. In summary, only the study by Van Esch, et al. (1962) provides even the barest hint of a dose-response relationship with reference to carcinogenesis.

Teratogenicity

The delivery into the world of a physically or mentally abnormal child is as great a tragedy as cancer. There is little information in the literature to suggest that lead has a teratogenic effect in man. Although there were numerous reports of a high incidence of stillbirths and miscarriages among women working in the lead trades, fetal anomalies were not described. It must be pointed out too that these women were probably exposed to much higher concentrations of lead than for even occupationally exposed men today. The more recent literature also is devoid of any references to teratogenic effects in man.

In experimental animals, on the other hand, lead has been shown repeatedly to have teratogenic effects. Early studies demonstrated this in chick embryos by injection of lead into the yolk sac (Catzione and Gray, 1941; Karnofsky and Ridgway, 1952). Teratogenesis has also been observed in rodents. These studies were done using high doses of lead given intravenously or intraperitoneally. For example, McClain and Becker (1975) used single interaperitoneal doses of 25 to 70 mg/kg in rats. They found that teratologic effects occurred when administration was on day 9. Administration later in pregnancy resulted in embryotoxicity (fetal resorption) but not in teratogenic effects. Carpenter and Ferm (1977) observed teratologic effects in hamsters following the administration of 50 mg/kg $Pb(NO_3)_2$ intravenously on day 8. Chronic administration of lead in the drinking water of pregnant rats at very high concentrations (up to 250 mg/l resulted in delayed fetal development and fetal resorption without teratologic effects (Kimmel, et al. 1976).

In summary, it seems that, in man, embryotoxicity precedes teratogenicity in the lead sensitivity scale. This is supported by historical experience in occupationally exposed women and by animal studies.

Mutagenicity

No information is available concerning mutagenicity of lead.

Reproductive Effects

As was indicated in the previous section, lead has been known to cause miscarriage and stillbirths in women working in the lead trades during the latter half of the 19th century and probably on into the early part of the 20th century. It is very difficult to estimate minimally toxic exposure for stillbirth and miscarriages because exposure data, e.g., PbB are lacking for women who experienced this problem. The minimally toxic level of exposure may actually be quite low. Lane (1949) reported on the outcome of 15 pregnancies incurred among 150 women working in an unspecified lead trade during World War II. Three of these women had miscarriages - an incidence seven times normal. Unfortunately the numbers were too small to be assigned statistical significance. Lead exposure was modest, air lead being 75 $\mu g/m^3$ and urinary lead excretion in men working with these women being 75 to 125 $\mu g/l$. A more recent Japanese study also is suggestive of miscarriages occurring among women with only modest exposure (Nogaki, 1958). These women were the wives of lead workers. Unfortunately, the actual level of lead exposure was not reported.

It has recently been reported that the incidence of premature fetal membrane rupture in term and preterm infants is much higher in a lead mining area of Missouri (17 percent) than in a Missouri urban area remote from lead mining activities (0.41 percent) (Fahim, et al. 1976). Maternal and fetal PbB's at birth also differed significantly for normal births vs. births with premature membrane rupture. Maternal and fetal PbB's for the normal deliveries were about 14 and 4 $\mu g/dl$ respectively whereas they were about 26 and 13 respectively for mothers and infants with membrane rupture. This provocative study needs confirmation. It is difficult to understand, for example, why fetal PbB should be so much lower than maternal PbB in all groups.

There is a possibility that lead affects fertility as well as the concept. Lancranjan, et al. (1975) reported that the significant levels of teratospermia occurred among men working in a lead storage battery factory. Their PbB's were 30 to 80 µg/dl. Although many studies have attempted to correlate semen quality with fertility, the extent to which abnormally-shaped sperms participate in fertilization is unclear. Experimental animal studies have shown reduced fertility of both maternal and paternal origin (Stowe and Goyer, 1971; Jacquet, et al. 1975).

There have been numerous conflicting reports concerning the occurrence of chromosomal aberrations in lymphocytes of lead-exposed workers. See, for example, O'Riordan and Evans (1974) and Forni, et al. 1976. The reason for these conflicting findings is not clear. DeKnudt, et al. (1977a) suggest that ancillary factors may be critical; for example, the level of calcium intake. They base this conclusion on the lack of correspondence between lead effects in two widely separated lead-using plants, one being a secondary lead smelter and the other being a plant manufacturing "tin" dishes. Lead exposures were roughly comparable PbB's were of the order of 45 - 100 µg/dl. Severe aberrations were found in one plant whereas no such effects were seen in the other. They further point out that no severe aberrations have been seen in at least some animal studies in which lead exposure was heavy and nutrition apparently adequatre (Jacquet, et al. 1977; De Knudt, et al. 1977b). The implications of chromosomal aberrations which have been reported are not known. A recent report by Wibberley, et al. (1977), which demonstrates a striking increased incidence of high placental lead associated with stillbirths or congenital malformations, further suggests that a relationship exists between intrauterine exposure to lead and reproductive casualty.

Renal Effects

There is considerable information in man concerning the renal effects of lead. Two distinctive effects occur, in both adults and children. One is reversible proximal tubular damage, which is seen mainly with short-term exposure. The other effect is reduced glomerular function which has generally been considered to be of a slow, progressive nature.

Tubular damage is manifested as the Fanconi triad of glycosuria, hypophosphatemia with phosphaturia, and generalized aminoaciduria. The last-named manifestation appears to occur more consistently than either glycosuria or phosphaturia. It was first described more than 20 years ago in lead smelter workers (Clarkson and Kench, 1956). In adults, the condition probably is uncommon at PbB's below 70 μg/dl. Thus, in a recent series of seven workers, all of whom had PbB's 70 μg/dl, with a range of 71-109, none had aminoaciduria or glycosuria. Significantly, five had hemoglobins below 12 g/dl (Cramer, et al. 1974). Similarly, in a series of 15 infants hospitalized for lead poisoning, and all having PbB's > 100 μg/dl at entry only three had aminoaciduria, with PbB's of 246, 299 and 798 μg/dl (Chisolm, 1968).

Reduced glomerular filtration with attendant rise in serus urea concentration is generally considered to be a progressive disease, implying prolonged lead exposure. It is accompanied by interstitial fibrosis, obliteration of glomeruli and vascular lesions (Morgan, et al. 1966). It occurs at relatively low levels of lead exposure, at least relative to the levels associated with aminoaciduria. For example, in Cramer's series of seven workers, none of whom had aminoaciduria, three had low renal clearance of inulin (90 ml/min/$1.73m^2$). In another study of eight men with occupational lead exposure (PbB's = 29-98), four had reduced glomerular filtration rates (Wedeen, et al. 1975). Of these four cases, one had a PbB of 48 µg/dl at entry. Tm_{PAH} was also reduced, indicating coexistent tubular damage. Among the other three cases, 2 had only a marginal depression of Tm_{PAH}.

From these and other studies, it appears that the kidney is sensitive to glomerular-vascular damage, with an imprecisely known threshold for effect which may be below PbB = 50 µg/dl.

Cardiovascular Effects

Dingwall-Fordyce and Lane (1963) reported an excess mortality rate due to cerebrovascular disease among lead workers. These workers were employed during the first quarter of the 20th century when lead exposure was considerably higher than it has been more recently. There was no similar elevated mortality among men employed more recently however. Similarly, in Cooper's more recent epidemiological study there was no excess mortality attributable to stroke or other diseases associated with hypertension or vasculopathy (Cooper and Gaffey, 1975; Cooper, 1978). It would appear from these studies that the vascular effects of lead only occur with heavy industrial lead exposure - probably in excess of what is encountered today.

There have been reports of heart failure (Kline, 1960) and of electrocardiographic abnormalities (Kosminder and Pentelenz, 1962) attributable to lead exposure. However, these cases have always involved clinical lead intoxication. It does not seem likely, therefore, that the heart is a critical target for lead effects.

Miscellaneous Effects

Sporadic reports of other biological effects of lead in man exist but, these are difficult to evaluate as to associated lead exposure. They have frequently been reported only at high exposure levels and only by one or two investigators. For example, Dodic, et al. (1971) reported signs of impaired liver function in 11 of 91 patients hospitalized for lead poisoning. No information was provided as to indices of lead exposure. Impairment of thyroid function has been reported in moonshine whiskey drinkers hospitalized for lead poisoning (Sandstead, et al. 1969). The degree of lead exposure was not clearly indicated, but it must have been high, judging from the fact that the men were hospitalized. Intestinal colic has long been recognized as a sign of lead in industrially exposed people. It probably also occurs in children with lead poisoning. Beritic (1971) reported that it occurs with PbB's as low as about 40 µg/dl. This seems unlikely since the cases he reported also were anemic, a condition associated with the considerably higher PbB's. A number of studies have suggested that a relationship exists between lead exposure and amyotrophic lateral sclerosis (ALS). The most recent report on this examined plasma lead levels in 16 cases of ALS and in 18 controls and found significant differences at the 0.05 level (Conraid, et al. 1978).

Finally, animal studies indicate that relatively high levels of lead exposure interfere with resistance to infectious disease (Hemphill, et al. 1971; Gainer, 1974). There are no reports of an abnormal infectious disease incidence among people with high lead exposure, however.

CRITERION FORMULATION

Existing Guidelines and Standards

Since lead is ubiquitous in the environment, several government agencies have become involved in regulating its use. The most recent action was taken by the Consumer Product Safety Commission (CPSC). In 1977 the CPSC lowered the maximum allowable concentration of lead in housepaint to 0.06 percent. At present the Occupational Saftey and Health Administration (OSHA) is preparing a set of regulations regarding occupational lead exposure. Similarly, the U.S. EPA has set an ambient air lead standard. The U.S. Food and Drug Administration also is due to hand down in September, 1978 new guidelines for the regulation of sources of lead in foods and cosmetics. Given the multimedia nature of lead exposure to man, it is essential that any action taken in regard to one source, such as water, be coordinated with similar actions being taken for other media such as air and diet.

Current Levels of Exposure

Approximately 1 percent of tapwater samples have been found to exceed the current standard of 50 µg/l. This is generally a problem in softwater areas, particularly where lead pipes convey the water supply to the tap from the surface connection. The contribution of the diet is approximately 200 µg/day for adults. For children (ages 3 months to 9 years) the diet contributes 40 to 200 µg of lead per day. On the basis of current information, it is impossible to judge how much dietary lead is attributable to the water used in food preparation. The concentration of lead in ambient air ranges from approximately 0.1 $\mu g/m^3$ in rural areas to as much as 10 $\mu g/m^3$ in areas of heavy automotive traffic.

Special Groups at Risk

In addition to these usual levels of exposure from environmental media, there exist miscellaneous sources which are hazardous. The level of exposure resulting from contact is highly variable. Children with pica for paint chips or for soil may experience elevation in blood lead ranging from marginal to sufficiently great to cause clinical illness. Certain adults may also be exposed to hazardous concentrations of lead in the workplace, notably in lead smelters and storage battery manufacturing plants. Again, the range of exposure is highly variable. Women in the workplace are more likely to experience adverse effects from lead exposure than men due to the fact that their hematopoietic system is more lead-sensitive than in men.

Basis and Derivation of Criterion

The approach that will be taken here in assessing the impact of lead in water on human health is basically the same as has been taken by the U.S. EPA (1977) for lead in air. The critical target organ or system must first be identified. Then, the highest internal dose of lead that can be tolerated without injury to the target organ must be specified. Finally, the impact of lead in water on the maximum tolerated internal dose must be estimated, as well as the likely consequences of specific reductions in the maximum allowable concentration of lead in water.

In identifying the critical organ or system, great reliance is placed on the concentration of lead in the blood (PbB) as an index of internal dose. Such an indirect measurement is necessary because of the multi-media character of lead intake. It is virtually impossible to measure total lead input in people in any meaningful way. To do so would require long-term balance studies because past experience has shown that intake and output fluctuate greatly from day to day. Furthermore, it would be necessary to conduct such studies on large numbers of free-living subjects, given the influences of chemical and physical variables in the numerous environmental forms of lead. Variables have a substantial influence on the rate and degree of lead uptake from the external environment. Some groups have proposed alternatives to PbB as a measure of internal dose, e.g., FEP and tooth lead. FEP is not suitable because it is a biological response to lead. As such, it is subject to influences other than lead, notably iron deficiency. Tooth lead is a potentially useful index of lead exposure, but with the present state of art being what it is, tooth lead is difficult to interpret. It only provides an integrated profile of past lead exposure. One is not able to say when the exposure occurred. It has the additional limitation of not being available on demand. Teeth are shed spontaneously only in childhood. Beyond all that is the fact that we have only a very small data base for dose-effect and dose-response using any measure of dose other than PbB. The use of PbB as a measure of internal dose is widely accepted, simply because nothing better is available.

Having specified that PbB is the best measure of internal dose currently available, the next question concerns the least PbB at which adverse health effects occur. Two recent documents (U.S. EPA, 1977a; WHO, 1977a) have been published in which judgments were rendered in this regard (Table 12). It will be noted that the estimates are strikingly similar. The estimated no-effects levels are based on limited populations and probably are lower to some undefinable degree in the total population at risk. The expert panels that made these estimates were largely composed of different individuals, although there was some overlap.
Slightly more information was available to the U.S. EPA panel than to the World Health Organization panel since it reviewed literature only through mid-1977 whereas the World Health Organization expert groups reviewed literature through much of 1976. In addition, the U.S. EPA performed statistical calculations based on the known distribution of blood lead levels in the United States.

Both sets of data in Table 12 are in error in one regard. They use the term "anemia" inappropriately under the "Effect" column. What they really mean is "decrement in hemoglobin." Anemia is a clinical term used to denote a degree of hemoglobin decrement which is below the normal range for that class of individuals, e.g., men or children.

The question that arises in considering Table 12 is which is the critical effect? Precisely the same issue confronted the U.S. EPA in its deliberations concerning establishment of a national ambient air quality standard for lead (42 FR 630979). It focused on the lead effects in children since they are more sensitive than adults.

TABLE 12

Summary of Lowest PbB's Associated with Observed Biological Effects in Various Population Groups[a]

Lowest observed effect level (μg Pb/100 ml blood)	Effect	Population group
10	ALAD inhibition	Children and adults
15 - 20	Erythrocyte protoporphyrin elevation	Women and children
25 - 30	Erythrocyte protoporphyrin elevation	Adult males
40	Increased urinary ALA excretion	Children and adults
40	Anemia	Children
40	Coproporphyrin elevation	Adults and children
50	Anemia	Adults
50 - 60	Cognitive (CNS) deficits	Children
50 - 60	Peripheral neuropathies	Adults and children
80 - 100	Encephalopathic symptoms	Children
100 - 120	Encephalopathic symptoms	Adults

No-detected effect levels in terms of PbB[b]

No detected effect level (μgPb/100 ml blood)	Effect	Population
10	Erythrocyte ALAD inhibition	adults, children
20-25	FEP	children
20-30	FEP	adult, female
25-35	FEP	adult, male
30-40	Erythrocyte ATPase inhibition	general
40	ALA excretion in urine	adults, children
40	CP excretion in urine	adults
40	Anaemia	children
40-50	Peripheral neuropathy	adults
50	Anaemia	adults
50-60	Minimal brain dysfunction	children
60-70	Minimal brain dysfunction	adults
60-70	Encephalopathy	children
80	Encephalopathy	adults

[a] U.S. EPA, 1977

[b] World Health Organ., 1977

Quite properly, it ruled that the maximum safe blood lead level for any given child should be somewhat lower than the threshold for a decline in hemoglobin level (40 µg Pb/dl). In considering how much lower this limit should be, the U.S. EPA cited the opinion of the Center for Disease Control, as endorsed by the American Academy of Pediatrics, that the maximum safe blood lead level for any given child should be 30 µg/dl. Based upon epidemiological and statistical considerations, the U.S. EPA estimated that if the geometric mean PbB were kept at 15 µg/dl, 99.5 percent of children would have PbB's $\leq$ 30 µg/dl. This position seems prudent and reasonable. It provides a substantial margin of safety which accommodates minor excursions in lead exposure due to adventitious sources. Controls on lead in obligatory media (e.g., air and water) do not of course protect children from the hazards of pica for lead-base paint chips or soil and dust contaminated with lead from such sources as fallout from the smoke zone of lead smelters. These, however, are separate problems which must be dealt with appropriately by responsible agencies.

In its deliberations concerning an ambient air lead standard, the U.S. EPA estimated that the contribution of sources other than air to PbB is 10 to 12 µg/dl. This is presumably composed overwhelmingly of dietary sources which, in turn, is composed of both food and water.

The next question concerns the contribution of water to lead exposure. It is unfortunate that only three useful studies of the interrelationship between PbB and lead in drinking water are available. There is an obvious need for more such work. Overall, the Moore, et al. (1977a) study, the one by Hubermont, et al. (1978), and the calculations made from U.S. EPA data collected in the Boston area (Greathouse and Craun, 1976) are credible because they are consistent with other information concerning the curvilinear relationship between PbB and air Pb. The implication of the equation describing the relationship between PbB and water lead is that with increasing lead in water the incremental rise in PbB becomes progressively smaller as with air lead vs. PbB and dietary lead vs. PbB (see section on "Contributions to Lead from Diet Versus Air to PbB"). The water lead vs. PbB relationship differs in one significant respect, however, from the air lead vs. PbB relationship in that the baseline PbB (0 water PbB) is independent of the contribution of water lead to PbB. Thus, regardless of whether one starts with a baseline PbB of 11 µg/dl, as was indicated in the Moore, et al. study or whether one starts at some other PbB level, e.g., 20 µg/dl, the add-on PbB from any given level in water will be the same. Such is not the case in the Azar analysis of air Pb vs. PbB (see Section on "Contributions of Lead from Diet vs. Air to PbB"). Here, the higher the baseline, the less the contribution of any specific air Pb. This is because log PbB (not PbB) is proportional to baseline PbB + log air concentration. Future research may provide better insight into whether this discrepancy is real and, if so, why. The question is of some practical importance. For instance, if you have a baseline PbB (no lead in water) of 30 µg/dl such as in a child acquiring lead from paint, it would be of some importance to know whether an additional increment of lead in water would have the same impact on PbB as it would in a child having a baseline

PbB of 10 μg/dl. An Azar-type model would suggest a lesser impact starting from the higher baseline PbB.

So far as a specific recommendation regarding a revised water standard for lead is concerned, one is tempted to duck the whole issue by simply recommending more research. However, that might defer the recommendation indefinitely. A position must be taken using available data. Beginning with the assumption that a PbB of 12 μg/dl is essentially attributable to food and water and that the average lead content of water consumed is 10 μg/l, approximately 5 ug Pb/dl blood (from Table 6) is attributable to the water that is used in food and beverage preparation and in direct consumption. If the water Pb were consistently consumed at the present Pb standard of 50 μg/l instead of at 10 μg/l, an additional contribution of approximately 3.4 μg/dl to PbB would result (8.57 - 5.13 from Table 6). This would yield a total PbB of 12 + 3.5 or 15.4 μg/dl, the approximate maximum geometric mean PbB compatible with keeping 99.5 percent of the population under PbB = 30 μg/dl. Thus, based on most recent data, the present water standard of 50 μg Pb/l may be viewed as representing the upper limit of acceptability. This criteria is based on empirical observation of blood lead in human population groups consuming their normal amount of water and food daily. Specific amounts of foods or dinking water consumed were not quantified, but it can be assumed that they reflect an average consumption of water, fish, shellfish, and other foods.

All the assumptions that have been made in arriving at an estimate of the impact of lead in water on PbB have been on the conservative side. For instance, unpublished data from the Commission of the European Communities suggest that the impact of lead in water on PbB is appreciably less than has been estimated from published data used in this document (personal communication from Alexander Berlin, Commission of the European Communities, Luxembourg)[1]. Furthermore, data (Table 13) from a study (Morse, et al. 1978) of the effect of lead in water on the PbB of a population of children in a relatively small town are reassuring. They indicate that among children whose water supply contained 50 to 180 µg Pb/l, PbB's averaged 17.2 µg/dl (P.J. Landrigan, Center for Disease Control, Atlanta, Georgia, personal communication).

TABLE 13

Relation of PbB to Lead in Water Among Children in Bennington, Vermont[a]

Concentration of Lead in Water (µg/l)	Number of Children	Mean Blood Lead Level (µg/dl)
50-59	14	18.9
60-69	8	16.9
70-79	10	15.0
80-89	4	18.5
100-109	3	16.0
110-119	2	21.5
130-139	2	16.0
170-179	3	15.0
Total	46	17.2

[a] Philip J. Landrigan, Center for Disease Control, Atlanta, personal communication.

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[1] Subsequent to the writing of this report, these data were submitted to the EPA by Dr. Berlin. They were studied and judged not to alter the conclusions arrived at in this document concerning PbB vs. lead in water (see Appendix I).

Finally, there remains the issue of the carcinogenic effects of lead. Using data from one species of laboratory animal (the rat) it was possible to construct a seemingly valid dose-response curve and to calculate a level of lead intake which would predict an incidence of cancer in 1:100,000 people. This calculated level of lead intake, 29 µg/kg of diet, poses some problems which must be confronted by the EPA Carcinogen Assessment Group. Since this estimate includes lead from all sources, its implications are beyond the scope of this document. It should be noted, however, that the International Agency for Research on Cancer, (IARC), Lyon, France considers the experimental animal evidence to be of dubious significance with regard to man (IARC, 1972). The IARC summary statement, quoted in part earlier in this document, is as follows:

> There is no evidence to suggest that exposure to lead salts causes cancer of any site in man. However, only one epidemiological study of the relationships between exposure to lead and the occurrence of cancer has been reported. It must be noted that the level of human exposure equivalent to the levels of lead acetate producing renal tumors in rats is 810 mg per day (550 mg Pb). This level appears to exceed by far the maximum tolerated dose for man.

REFERENCES

Albert, R.E., et al. 1974. Follow-up of children overexposed to lead. Environ. Health Perspect. Exp. Issue No. 7: 33.

Alexander, F.W., et al. 1973. The uptake and excretion by children of lead and other contaminants. Page 319 in Proc. Int. Symp. Environ. Health. Aspects of Lead. Amsterdam, 2-6 Oct., 1972. Comm. Eur. Commun. Luxembourg.

Alvares, A.P., et al. 1975. Drug metabolism in normal children, lead poisoned children and normal adults. Clin. Pharm. Ther. 17: 179.

Angle, C.R., et al. 1975. Lead and iron deficiency. In D.D. Hemphill, ed. Trace substances in environmental health. IX. University of Missouri Press.

Araki, A.R. 1976. Peripheral neuropathy at low level industrial lead exposures. Scand. Jour. Work Environ. Health. 2: 225.

Azar, A., et al. 1973. Review of lead studies in animals carried out at Haskell Laboratory - two-year feeding study and response to hemorrhage study. Page 199 in Proc. Int. Symp. Environ. Health, Aspects of Lead. Amsterdam, 2-6 Oct., 1972. Comm. Eur. Commun. Luxembourg.

Azar, A., et al. 1975a. An epidemiologic approach to community air lead exposure using personal air samplers. Environ. Qual. Safe. Suppl. II: Leas 152.

Azar, A., et al. 1975b. An epidemiologic approach to community air lead exposure using personal air samplers. Environ. Qual. Safe. Suppl. II: Leas 254.

Barltrop, D. 1966. The prevalence of ica. Am. Jour. Dis. Child. 112: 116.

Barltrop, D., et al. 1974. Significance of high soil lead concentrations for childhood lead problems. Environ. Health Perspect. Exp. Iss. 7: 75.

Barltrop, D., and H.E. Khoo. 1975. The influence of nutritional factors on lead absorption. Postgrad. Med. Jour. 51: 795.

Barltrop, D., and F. Meek. 1975. Absorption of different lead compounds. Postgrad. Med. Jour. 51: 805.

Barry, P.S.I. 1975. A comparison of concentrations of lead in human tissues. Br. Jour. Ind. Med. 32: 119.

Beattie, A.D., et al. 1972a. Environmental lead pollution in an urban soft-water area. Br. Med. Jour. 2: 4901.

Beattie, A.D., et al. 1975. Role of chronic, low level lead exposure in the aetiology of mental retardation. Lancet I: 589.

Beritic, T. 1971. Lead concentration found in human blood in association with lead colic. Arch. Environ. Health. 23: 289.

Berk, P.D., et al. 1970. Hemotologic and biochemical studies in a case of lead poisoning. Am. Jour. Med. 43: 137.

Betts, P.R., et al. 1973. Lead intoxication in children in Birmingham. Br. Med. Jour. 1: 402.

Bicknell, J., et al. 1968. Lead in mentally retarded children. Jour. Mental Def. Res. 12: 282.

Boggess, W.R., ed. 1978. Lead in the encironment, NSF/RA-770214.

Bolinowska, W.J.,et al. 1967. Triethyllead in the biological material in cases of acute terathyllead poisoning. Arch. Toxicol. 22: 278.

Boyland, E., et al. 1962. The induction of renal tumors by feeding lead acetate to rats. Br. Jour. Cancer 16: 283.

Bull, R.J., et al.1978. Delays in the postnatal increase of cerebral cytochrome concentrations in lead-exposed rats. Neuropharmacology. In press.

Byers, R.K., and E.E. Lord. 1943. Late effects of lead poisoning on mental development. Am. Jour. Dis. Child. 66: 471.

Carpenter, S.J., and V.H. Ferm. 1977. Embryopathic effects of lead in the hamster. Lab. Invest. 37: 369.

Carson, T., et al. 1974. Slowed learning in lambs prenatally exposed to lead. Arch. Environ. Health 29: 154.

Catzione, O., and P. Gray. 1941. Experiments on chemical interference with the early morphogenesis of the chick. II. The effects of lead on the central nervous system. Jour. Exp. Zool. 87: 71.

Center for Disease Control. 1977. Surveillance of childhood and lead poisoning -United States. Morbid. Mortal Week. Rep. 26: 48.

Chisolm, J.J. 1968. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. Jour. Pediatr. 73: 1.

Chisolm, J.J., et al. 1975. Dose-effect and dose-response relationships for lead in children. Jour. Pediatr. 87: 1152.

Clarkson, T.W., and J.E. Kench. 1956. Urinary excretion of amino acids by men absorbing heavy metals. Biochem. Jour. 62: 361.

Conradi, S., et al. 1978. Jour. Neurol. Neurosburg. Psychiatry 41: 389.

Cooper, W.C. 1978. Mortality in workers in lead production facilities and lead battery plants during the period 1971-1975. A report to International Lead Zinc Research Organization, Inc.

Cooper, W.C., and W.R. Gaffey. 1975. Mortality of lead workers. Jour. Occup. Med. 17: 100.

Coulston, F., et al. 1962. The effects of continuous exposure to airborn lead. 2. Expose of man to particular lead at a level of 10.9 $\mu g/m^3$. Final Rep. U.S. Environ. Prot. Agency.

Cramer, K., et al. 1974. Renal ujtrastructure renal function and parameters of lead toxicity in workers with different periods of lead exposure. Br. Jour. Ind. Med 31: 113.

Crofton, K.M., et al. 1978. Developmental delays in exploration and locomotor activity in male rats exposed to low level Pb. Submitted to Science.

DeKnudt, Gh. 1977a. Chromosomal aberrations in workers professionally exposed to lead. Jour. Toxicol. Environ. Health 3: 885.

DeKnudt, Gh. et al. 1977b. Chromosomal abnormalities in lymphocytes from monkeys poisoned with lead. Mutat. Res. 45: 77.

De la Burde, B., and M.S. Choate. 1972. Does asymptomatic lead exposure in children have late sequelae? Jour. Pediatr. 81: 108.

De la Burde, B., and M.S. Choate. 1975. Early asymptomatic lead exposure and development at school age. Jour. Pediatr. 87: 638.

Dingwall-Fordyce, J., and R.E. Lane. 1963. A follow-up study of lead workers. Br. Jour. Ind. Mech. 30: 313.

Docid, S., et al. 1971. Stanjc jetre w pojedinih profesionalnih intosksikaiija In: III Jugoslavanski Kongres Medicine Dela, Ljubljana, 1971.

Eisenbud, M., and M.E. Wrenn. 1970. Radioactivity studies. Annual Rep. NYO-30896-10. Natl. Tech. Inf. Serv. 1: 235. Springfield, Va.

Elwood, P.C., et al. 1976. Dependence of blood-lead on domestic water lead. Lancet 1: 1295.

Erenberg, G.S., et al. 1974. Lead neuropathy and sickle cell disease. Pediatr. 54: 438.

Fahim, M.S., et al. 1976. Effects of subtoxic lead levels on pregnant women in the state of Missouri. Res. Commun. Chem. Pathol. Pharmacol. 13: 309.

Forbes, G.B., and J.C. Reina. 1974. Effect of age on gastrointestinal absorption (Fe, Sr, Pb) in the rat. Jour. Nutr. 102: 647.

Forni, A., et al. 1976. Initial occupational exposure to lead. Arch. Environ. Health. 31: 73.

Gage, J.C., and M.HY. Litchfield. 1969. The migration of lead from paint films in the rat gastrointestinal tract. Jour. Oil. Col. Chem. Assoc. 52: 236.

Gainer, J.H. 1974. Lead aggravates viral disease and represses the antiviral activity of interferon inducers. Environ. Health Perspect. Exp. 7: 113.

Gant, V.A. 1938. Lead poisoning. Ind. Med. 7: 679.

Garber, B.T., and E. Wei. 1974. Influence of dietary factors on the gastrointestinal absorption of lead. Toxicol. Appl. Pharmacol. 27: 685.

Granick, J.L., et al. 1973. Studies in lead poisoning. II. Correlation between the ratio of activiated to inactivated aminolevulinic acid dehydratase of whole blood and the blood lead level. Biochem. Med. 8: 149.

Greathouse, D.G., and Craun, G.F. 1976. Epidemiologic study of the relationship between lead in drinking water and blood lead levels. Page 9 in D.D. Hemphill, ed. Trace substances in environmental health. X. University of Missouri Press. p. 9.

Greathouse, D.G., and G.F. Craun. 1978. Cardiovascular disease study - occurence of unorganies in household tap water and relationships to cardiovascular mortality rates. In D.D. Hemphill, ed. Trace substances in environmental health. University of Missouri Press. To be published.

Haeger-Aronsen, B. 1971. An assessment of the laboratory tests used to monitor the exposure of lead workers. Br. Jour. Ind. Med. 28: 52.

Haeger-Aronsen, B., et al. 1974. Effect of lead on -aminolevulinic acid dehydratase activity in red blood cells. Arch. Environ. Health 29: 150.

Hammond, P.B. 1977a. Exposure of humans to lead. Ann. Rev. Pharmacol. Toxicol. 17: 197.

Hammond, P.B., et al. 1977. Sources of lead in children. Progress Report NSF/RANN Grant No. AEN-7414760.

Hammond, P.B., and A.L. Aronson. 1964. Lead poisoning in cattle and horses in the vicinity of a smelter. Ann. N.Y. Acad. Sci. 111: 595.

Harris, R.W., and W.R. Elsea. 1967. Ceramic glaze as a source of lead poisoning. Jour.AMA 303: 344.

Hemphill, F.E., et al. 1971. Lead suppression of mouse resistance of Salmonella typhimurium. Science 172: 1031.

Hernberg, S., et al. 1967. Nonrandom shortening of red cell survival times in men exposed to lead. Environ. Res. 1: 247.

Heusgem, C., and J. DeGraeve. 1973. Importance de l'apport ailmentaire en plomb dand l'est de la Belgique. Page 85 in Proc. Int. Symp. Environ. Health Aspects of Lead, Amsterdam, 2-6 October, 1972. Comm. Eur. Commun. Luxembourg.

Hopkins, D.R., and W.N. Houk. 1976. Federally-assisted screening projects for childhood lead poisoning control. Am. Jour. Pub. Health. 66: 485.

Horiuchi. K., et al. 1956. Studies on the industrial lead poisoning. I. Absorption, transportation, deposition and excretion of lead. 2. A study on the lead content in daily food in Japan. Osaka City, Med. Jour. 3: 84.

Horiuchi, K., and I. Takada. 1954. Studies on the industrial lead poisoning. I. Absorption, transportation, deposition and excretion of lead. 1. Normal limits of lead in the blood, urine and feces among healthy Japanese urban habitants. Osaka City, Med. Jour. 1: 117.

Hubermont, G., et al. 1978. Placental transfer of lead, mercury and cadmium in women living in a rural area. Int. Arch. Occup. Environ. Health 41: 117.

Hunt, W.F., Jr., et al. 1971. A study in trace element pollution of air in seventy-seven midwestern cities. Page 56 _in_ D.D. Hemphill, ed. Trace substances in environmental health. IV. University of Missouri Press.

IARC. 1972. Evaluation of carcinogenic risk of chemicals to man. Int. Agency Res. Cancer. World Health Organ. Lyon, France.

Jacquet, P., et al. 1975. Progress report on studies into the toxic action of lead in biochemistry of the developing brain and on cytogenetics of post meiotic germ cells. Economic Community of Europe, Contract No. 080-74-7, Brussels, Belgium.

Jacquet, P., et al. 1977. Cytogenetic investigations on mice treated with lead. Jour. Toxicol. Environ. Health 2: 619.

Jandl, J.H., et al. 1959. Transfer of iron from serum iron-binding protein to human reticulobytes. Jour. Clin. Invest. 38: 161.

Jennett, A.C., et al. 1978. Lead in the environment. NSF/RA-880215. W.R. Boggess, ed.

Joselow, M.M., and J.D. Bogden. 1974. Lead content of printed media. (Warning: spitballs may be hazardous to your health.) Am. Jour. Pub. Health 64: 238.

Karnofsky, D.A., and L.P. Ridgway. 1952. Production of injury to the central nervous system of the chick embryo by lead salts. Jour. Pharmacol. Exp. Therap. 104: 176.

Kehoe, R.A. 1961. The metabolism of lead in man in health and disease. The Harben Lectures, 1960. Jour. R. Inst. Publ. Health Hyg. 34: 1.

Kimmel, C.A., et al. 1976. Chronic lead exposure: Assessment of developmental toxicity. Teratology 13: 27 A (abstract).

Klein, M., et al. 1970. Earthenware containers as a source of fatal lead poisoning. Case study and public-health considerations. New England Jour. Med. 385: 669.

Kline, T.S. 1960. Myocardial changes in lead poisoning. AMA Jour. Dis. Child. 99: 48.

Kneip, T.J., et al. 1974. New York University Inst. Environ. Med. Contract NO. CPSC-C-074-153.

Kobayashi, N., and T. Okamoto. 1974. Effects of lead oxide on the induction of lung tumors in Syrian hamsters. Jour. Natl. Cancer Inst. 52: 1605.

Kosmider, S., and T. Pentelenz. 1962. Zmiany elektro kardiografyficzne u. starszychosol, 2. prezwleklym zauo-dowym zatruciem olowiem. Pol. Arch. Med. Wein 32: 437.

Kostial, K., et al. 1971. Lead absorption from the intestine in newborn rats. Nature (Lond.) 233: 564.

Kotok, D. 1972. Development of children with elevated blood lead levels: A controlled study. Jour. Pediatr. 80: 57.

Lamm, S.H., and J.F. Rosen. 1974. Lead contamination in milk fed to infants: 1972-1973. Pediatrics 53: 137.

Langerwerff, J.V., and A.W. Specht. 1970. Contamination of roadside soil and vegetation with cadmium, nickle, lead and zinc. Environ. Sci. Technol. 4: 583.

Lancranjan, I., et al. 1975. Reproductive ability of workmen occupationally exposed to lead. Arch. Environ. Health 30: 396.

Landrigan, P.J., et al. 1975. Epidemic lead absorption near an ore smelter. The role of particulate lead. New England Jour. Med. 292: 123.

Landrigan, P.J., and E.L. Baker. 1976. Increased lead absorption with aremia and slowed nerve conduction in children near a lead smelter. Pediatrics 89: 904-910.

Lane, R.E. 1949. The care of the lead worker. Br. Jour. Ind. Med. 6: 1243.

Lansdown, R.G., et al. 1974. Blood-lead levels, behavior and intelligence. A population study. Lancet I. 538.

Laug, E.P., and F.M. Kunze. 1948. Penetration of lead through skin. Jour. Ind. Hyg. Toxicol. 30: 256.

Lilis, R., et al. 1977. Lead effects among secondary lead smelter workers with blood levels below 80 µg/100 ml. Arch. Environ. Health Nov. 1977. 256.

Mao, P., and J.J. Molnar. 1967. The fine structure and histochemistry of lead-induced renal tumors in rats. Am. Jour. Pathol. 50: 571.

Maxfield, M.E., et al. 1972. Effect of lead on blood regeneration following acute hemorrhage in dogs. Am. Ind. Hyg. Assoc. Jour. 33: 326.

McCabe, L.J. 1970. Metal levels found in distribution samples. AWWA Seminar on Corrosion by Soft Water. Washington, D.C.

McCauley, P.T., et al. 1978. Association of alterations in energy metabolism with lead-induced delays in rat cerebral cortical development. Neuropharmacology. In press.

McClain, R.M., and B.A. Becker. 1975. Teratogenicity, fetal toxicity and placental transfer of lead nitrate in rats. Toxicol. Appl. Pharmacol. 31: 72.

McNeil, J.L., et al. 1975. Evaluation of long-term effects of elevated blood lead concentrations in asymptomatic children. Arhiv. Rig. Rada. Toksikol. 14: 97.

Meredith, P.A., et al. 1977. Delta-aminolaevulinic acid metabolism in normal and lead-exposed humans. Toxicology 9: 1.

Milburn, H., et al. 1976. An investigation of lead workers for subclinical effects using three performance tests. Ann. Occup. Hyp. 19: 239.

Millar, J.A., et al. 1970. Lead and ALAD (a-aminolevulinic acid dehydratase) levels in mentally retarded children and in lead poisoned suckling rats. Lancet 2: 695.

Mitchell, D.G., and K.M. Aldous. 1974. Lead content of foodstuffs. Environ. Health Perspect. Exp. Issue 7: 59.

Moore, M.R., et al. 1977a. Contribution of lead in water to blood-lead. Lancet II: 661.

Moore, M.R., et al. 1977b. A retrospective analysis of blood-lead in mentally-retarded children. Lancet I: 717.

Mooty, Ed. M., et al. 1975. Relationship of diet to lead poisoning in children. Pediatrics 55: 636.

Morgan, B.B., and J.D. Repko. 1974. In C. Xintaras, et al. eds. Behavioral toxicology. Early detection of occupational hazards. U.S.Dep. Health Edu. Welfare. Washington, D.C.

Morgan, J.M., et al. 1966. Nephropathy in chronic lead poisoning. Arch. Int. Med. 118: 17.

Morse, D.L., et al. 1978. Accepted for publication, Amer. Jour. Pub. Health.

Murthy, G.M., and U.S. Rhea. 1971. Cadmium, copper, iron, lead, manganese and zinc in evaporated milk, infant products and human milk. Jour. Dairy Sci. 54: 1001.

National Academy of Sciences/National Research Council. 1972a. Airborne lead in perspective. Washington, D.C.

National Academy of Sciences/National Research Council. 1972b. Airborne lead in perspective. Washington, D.C.

National Academy of Sciences/National Research Council. 1977. Drinking water and health. Washington, D.C.

Needleman, H.L., et al. 1978. Neurophysiological dysfunction in children with "silent" lead exposure. Pediat. Res. 12: 374 (Abstr. 63).

Nelson, W.C., et al. 1973. Mortality among orchard workers exposed to lead arsenate spray: a cohort study. Jour. Chron. Dis. 26: 105.

Nogaki, K. 1958. On action of lead on body of lead refinery workers: Particularly conception, pregnancy and parturition in case of females and their newborn. Excerp. Med. XVII. 4: 2176.

Nordman, C.N. 1975. Environment lead exposure in Finland. A study on selected population groups. Ph.D. thesis. University of Helsinki.

O'Riordan, M.L., and H.J. Evans. 1974. Absence of significant chromosome damage in males occupationally exposed to lead. Nature (Lond.) 247: 50.

Oyasu, R., et al. 197-. Induction of cerebral gliomas in rats with dietary lead subacetate and 2-acetylaminofluorene. Cancer Res. 30: 1248.

Perion, J., and C.B. Ernhart. 1974. The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. Jour. Learn. Dis. 7: 26.

Perlstein, M.A., and R. Attala. 1966. Neurologic sequelae of plumbism in children. Clin. Pediat. 6: 266.

Piddington, S.K., and J.M. White. 1974. The effect of lead on total globin and a and B chain synthesis; in vitro and in vivo. Br. Jour. Haematol. 27: 415.

Prerovska, I., and J. Teisinger. 1970. Excretion of lead and its biological activity several years after termination of exposure. Br. Jour. Ind. Med. 27: 352.

Prpic-Majic, D., et al. 1973. Delta-aminolevulinic acid dehydratase activity, lead blood levels, and the reticulocyte count. Environmental health aspects of lead. Proc. Symp. held in Amsterdam, Holland, Oct. 2-6, 1972. Comm. Eur. Commun. Luxembourg.

Pueschel, S.M., et al. 1972. A screening and follow up study of children with an increased lead burden. Jour. Am. Med. Assoc. 333: 462.

Rabinowitz, M.B., et al. 1973. Lead metabolism in the normal human: stable isotope studies. Science 182: 725.

Rabinowitz, M.B., et al. 1974. Studies of human lead metabolism by use of stable isotope tracers. Environ. Health Perspect. Exp. Issue 7: 145.

Rastogi, S.C., and J. Clausen. 1976. Absorption of lead through the skin. Toxicol. 6: 371.

Rhyne, B.C., and R.A. Goyer. 1971. Cytochrome content of kidney mitochondria in experimental lead poisoning. Exp. Mol. Pathol. 14: 386.

Roe, F.J.C., et al. 1965. Failure of testosterone or xanthopterin to influence the induction of renal neoplasms by lead in rats. Br. Jour. Cancer 19: 860.

Roels, H.A., et al. 1975. Response of free erythrocyte porphyrin and urinary a-aminolevulinic acid in men and women moderately exposed to lead. Int. Arch. Arbeitsmed. 34: 97.

Roels, H.A., et al. 1978. Lead and cadmium absorption among children near a nonferrous metal plant. A follow-up study of a test case. Environ. Res. 15: 290.

Sachs, H.K. 1974. Effects of a screening program on changing patterns of lead poisoning. Environ. Health Perspect., Exp. Issue 7: 41.

Sandstead, H.H., et al. 1969. Lead intoxication and the thyroid. Arch. Int. Med. 123: 632.

Sassa, S., et al. 1973. Studies in lead poisoning. I. Microanalysis of erythrocyte protoporphyrin levels by spectrophotometry in the detection of lead poisoning in the subclinical range. Biochem. Med. 8: 135.

Schroeder, H.A., et al. 1961. Abnormal trace metals in man: Lead. Jour. Chronic Dis. 14: 408.

Secchi, G.C., et al. 1971. Ricerche sull'attivita ALA-deidrasica eritrocitaria di soggetti non eposti a contatto lrofessionale con plombo ed abitanti in zone ruralied urbane. Med. Lav. 62: 435.

Secchi, G.C., et al. 1974. Delta-aminolevulinic acid dehydratase activity in erythrocytes and liver tissue in man. Arch. Environ. Health 28: 130.

Selander, S., and K. Cramer. 1970. Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Br. Jour. Ind. Med. 27: 28.

Seppalainen, A.M., et al. 1975. Subclinical neuropathy at "safe" levels of lead exposure. Arch. Environ. Health 30: 180.

Six, K.M., and R.A. Goyer. 1970. Experimental enhancement of lead toxicity by low dietary calcium. Jour. Lab. Clin. Med. 76: 933.

Six, K.M., and R.A. Goyer. 1972. The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. Journ. Lab. Clin. Med. 79: 128.

Smith, F.L., et al. 1938. The early diagnosis of acute and latent plubmism. Am. Jour. Clin. Pathol. 8: 471.

Sobel, A.E., et al. 1938. Influence of dietary calcium and phosphorous upon action of vitamin D in experimental lead poisoning. Proc. Soc. Exp. Biol. Med. 38: 435.

Stowe, H.D., and R.A. Goyer. 1971. The reproductive ability and progeny of F_1 lead-toxic rats. Fertil. Steril. 22: 755.

Strand, L.J., et al. 1972. The induction of d-aminolevulinic acid synthetase in cultured liver cells. Jour. Biol. Chem. 247: 2820.

Suketa, Y., et al. 1975. Changes in hepatic -aminolevulinic acid in lead-intoxicated rats. Jour. Toxicol. Environ. Health. 1: 127.

Tepper, L.B., and L.S. Levin. 1972. A survey of air and population lead levels in selected American communities. Final report to the U.S. EPA.

Ter Haar, G.L., and R. Aronow. 1974. New information on lead in dirt and dust as related to the childhood lead problem. Environ. Health Perspect. Exp. Issue 7: 83.

Thompson, J.A. 1971. Balance between intake and output of lead in normal individuals. Br. Jour. Ind. Med. 28: 189.

Tola, S. 1973. Effect of blood lead concentration, age, sex, and exposure time on the erythrocyte d-aminolevulinic acid dehydratase activity. Work Environ. Health 10: 26.

Tola, S., et al. 1973. Parameters indicative of absorption and biological effect in new lead exposure: A prospective study. Br. Jour. Ind. Med. 30: 134.

U.S. EPA. 1977a. Air quality criteria for lead. Pub. No. EPA - 600/8-77-017. U.S. Environ. Prot. Agency.

U.S. EPA. 1977b. Air quality criteria for lead. Pub. NO. EPA-600/8-77-017. U.S. Environ. Prot. Agency.

U.S. EPA. 1977b. Air quality criteria for lead. Pub. No. EPA-600/8-77-017. U.S. Environ. Prot. Agency.

U.S. EPA. 1977c. Air quality criteria for lead. EPA Pub. No. 600/8-77-017. U.S. Environ. Prot. Agency.

U.S. Food and Drug Administration. 1975. Compliance Program Evaluation. FY-1947. Heavy metals in foods survey. Bur. Foods. Washington, D.C.

Van Esch, G.J., et al. 1962. The induction of renal tumors by feeding basic lead acetate to rats. Br. Jour. Cancer 16: 289.

Van Esch, G.J., and R. Kroes. 1969. The induction of renal tumors by feeding basic lead acetate to mice and hamsters. Br. Jour. Cancer 23: 765.

Wedeen, R.P., et al. 1975. Occupational lead nephropathy, Am. Jour. Med. 59: 630.

Wetherill, G.W., et al. 1974. Proc. Int. Symp. Paris, France, June, 1974. Comm. Eur. Commun., U.S. Environ. Prot. Agency, World Health Organ.

Wibberley, D.J., et al. 1977. Jour. Med-Genetics 14: 339.

World Health Organization. 1977. Environmental health criteria 3 lead. Geneva.

Wong, C.S., and P. Berrang. 1976. Contamination of tap water by lead pipe and solder. Bull. Environ. Contam. Toxicol. 15: 530.

Ziegler, E.E., et al. 1978. Absorption and retension of lead by infants. Pediatr. Res. 12: 29.

Zielhuis, R.L. 1975. Dose response relationships for inorganic lead. I. Biochemical and haematological responses. II. Subjective and functional responses. Chronic sequelea. No-response levels. Int. Arch. Occup. Health 35: 1, 19.

Zollinger, H.U. 1953. Durch Chronische Bleivergiftung Erzeugte Nierenadenome und Carcinoma bei Ratten und Ihre Beziehungen zu Den Entsprechenden Neubildung des Menschen. (Kidney adenomas and carcinomas in rats caused by chronic lead poisoning and their relationship to corresponding human neoplasma). Virchow Arch. Pathol. Anat. 323: 694.

Zurlo, N., and A.M. Griffini. 1973. Le plomb dans les aliments et les boissons consommes a Milan. *In* Proc. Int. Symp. Environ. Health. Aspects of Lead. Amsterdam, 2-6 Oct., 1972. Comm. Eur. Commun. Luxembourg.

APPENDIX I

Summary of "Research of PbB vs. Lead in Drinking Water in Europe" as Presented by A. Berlin, et al. Commission of the European Communities.

Results of the research examined in the Commission of the European Communities (CEC) paper are summarized in Tables I-1 and I-2. The data presented in Table I-1 are equations developed by the authors concerning the relationship of blood lead (PbB) to water lead (PbW). Table I-2 consists of calculations of the contribution of 100 ug Pb/l of water to PbB (as ug/dl). Some of these calculations were made by Berlin, et al. interpolating from data points in the articles cited. Others were made using the equations provided by the authors of the articles cited.

Three types of equations are presented:

(1) $PbB = a + b\ PbW$

(2) $PbB = a + \log PbW$

(3) $PbB = a + \sqrt[3]{PbW}$

In all cases "a" is the baseline expressing PbB at PbW = 0. Of these three mathematical relationships, the third appears to be the most valid for two reasons: (1) the largest number of subjects are involved in studies using this equation, and (2) it corresponds to the analysis of U.S. EPA data (Greathouse and Craun, 1976) as cited in the lead criterion document, which also involved a very large number of subjects. Moreover calculations made of PbB vs.

TABLE I-1

Relationships between PbW and PbB[a]

Relationship	Remarks	Reference
PbB = 0.018 PbW + 22.9	r = 0.417 PbW = µg/l PbB = µg/100 ml First morning flush	Addis and Moore (1974)
PbB = 0.76 + 0.15 PbW	PbW and PbB in µmol/l r = 0.58, first morning flush	Moore (1977a)
PbB = 0.80 + 0.20 PbW	r = 0.52, running sample	
PbB = 0.533 + 0.675 ^{3} PbW	PbW and PbB in µmol/l first morning flush	Moore, et al. (1977)
PbB = 0.304 + 1.036 ^{3} PbW	running sample	
PbB = 9.62 + 1.74 log PbW	PbW in µg/l PbB in µg/100ml first morning flush	Lauwerys, et al. (1977)
PbB = 0.8 + 0.19 PbW	PbW and PbB in µmol/l first morning flush	Moore (1977b)
PbB = 0.8 + 0.53 PbW	full flush (paired samples)	
PbB = 19.6 + 7.2 PbW	PbW in ppm, PbB in µg/100ml first morning flush	Elwood, et al. (1976)
PbB = 20.7 + 12.6 PbW	As above. Re-evaluated data	Beattie, et al. (1976)

[a] Berlin, et al. (1978).

TABLE I-2

Increment in PbB for an Increase of 100 µg/l in PbW (for Concentrations around 100 µg/l)[a]

Increment in PbB	Remarks	Reference
1.3 µg/100ml	For running sample (linear interpolation) 20-1040 µg/l PbW	De Graeve, et al. (1975)
1.2 µg/100ml	First flush (linear interpolation) 10-250 µg/l PbW	Beattie, et al. (1972)
3.4 µg/100ml	For running sample (linear interpolation) 10-250 µg/l PbW	Covell (1975)
3.3 µg/100ml	For first flush (linear interpolation) 35-350 µg/l PbW	Addis, et al. (1974)
1.8 µg/100ml	Using the linear equation derived by the authors	Addis, et al. (1974)
2.0 µg/100ml	Using the linear equation derived by the author for running water samples.	Moore (1977a)
6.0 µg/100ml	Using the non-linear equation derived by the authors for running water samples.	Moore, et al. (1977)
3.9 µg/100ml	Using the non-linear equation derived by the authors for first morning flush.	Moore, et al. (1977)
0.83 µg/100ml	Using the log equation derived by the authors	Lauwerys, et al. (1977)
	In view of the low PbW value, the extrapolation is uncertain.	Vos, et al. (1977)
1.9 µg/100ml	Using the linear equation derived by the authors for morning flush	Moore, et al. (1977)
5.3 µg/100ml	Using the linear equation derived by the authors for full flush	Moore, et al. (1977)
0.72 µg/100ml	Using the linear equation derived by the authors for morning flush.	Elwood, et al. (1976)
1.3 µg/100ml	Using the re-evaluated linear equation derived by the authors for morning flush.	Beattie, et al. (1976)

[a] Berlin, et al. (1978).

PbW using the EPA data were for females aged 20 to 50, a sub-population which probably gets a larger proportion of its water from the domestic supply than the population at large. In that regard, the only comparable population was 70 pregnant female subjects in the study of Hubermont, et al. (1978) cited in the CEC document as Lauwreys, et al. (1977).

In summary, of the studies cited in the CEC document, most weight should probably be given to the Moore, et al. (1977) citation, on the basis of large numbers of samples of water and study subjects, and to the Hubermont, et al. (1978) study on the basis of a substantial number of subjects which were probably partaking of more of the domestic water supply than other sub-classes by virtue of pregnancy and sex.

So far as the actual calculations in Table I-2 are concerned, there is one error. The CEC document calculates that the equation of Hubermont, et al. (1978) (cited as Lauwreys, et al. 1977) would predict that PbW at 100 μg/l would result in a PbB contribution of 0.83 μg/dl. The error is obvious. In the equation, the PbB contribution of water is given by PbB = 1.74 log PbW. In fact, 0.83 = 1.74 log 3, not 1.74 log 100. The correct calculation is PbB = 1.74 X 2 = 3.48, since log 100 = 2.

Of the 13 estimates of PbB vs. PbW in Table I-2, only 5 could be verified. These were Addis, et al. (1974) (interpolation), Addis, et al. (1974) using authors' equation, Moore (1977a) using author's equation, Beattie, et al. (1976) using author's equation, and Moore, et al. (1977), non-linear morning flush. Of the remaining nine, one was miscalculated by CEC and the remaining eight could not be verified by this author because the paper was unavailable (Covell, 1975; Elwood, 1976), or because the necessary data were not in the paper (De Graeve, et al. 1975; Moore, et al. 1977 using non-linear equation for running water; Moore, et al. 1977 using linear equation for morning flush and running water calculations), or because it was not possible to see how CEC made an interpolation from the data cited (Beattie, et al. 1972).

In summary, the two most credible studies among the nine actually scrutinized in this addendum were the very ones utilized in the criterion document for lead. Of the two reviewed by the CEC but not examined at the time of this writing, (Covell, 1975; Elwood, 1976), one was reviewed prior to development of the criterion document and rejected on the basis of the seemingly inappropriate use of a linear regression model (see section on Contributions of Lead from Diet vs. Air to PbB). It is therefore concluded that information provided by CEC does not alter the evaluations made in the criterion document.

REFERENCES FOR APPENDIX I

Addis, C., and M. R. Moore. 1974. Lead levels in the water of suburban Glasgow. Nature 252: 120.

Beattie, A.D., et al. 1976. Blood lead and domestic water lead. Lancet 2: 200.

Beattie, A.D., et al. 1972. Environmental lead pollution in an urban soft-water area. Br. Med. Jour. 491.

Berlin, A., et al. 1978. Research on lead in drinking water in Europe. Comm. Eur. Commun.

Covell, B. 1975. Lead content in household water in Edinburgh. Health Bull. 33: 114.

De Graeve, J., et al. 1975. Plombemie d'une population adulte de l'Est de la Belgique. Rev. Epidem. Med. Soc. et Sante Publ. 23: 131.

Elwood, P.C., et al. 1976. Dependence of blood lead on domestic water lead. Lancet 1: 1295.

Lauwerys, R., et al. 1977. Influence of contamination of water by lead on exposure of pregnant mothers and their newborns. (Manuscript in preparation.)

Moore, M.R. 1977a. Lead in drinking water in soft water areas - health hazards. Sci. Total Environ. 7: 109.

Moore, M.R. 1977b. Materno-foetal lead studies. Personal communication.

Moore, M.R., et al. 1977. The contribution of lead in drinking water to blood lead. Lancet 2: 661.

Vos, M., et al. 1977. Een orienterend onderzoek naar de correlatie tussen watermetalen in bloedmetalen in de gemeenten Hoensbroek en Brunssum. In press.

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